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# ARCHIVES of INTERNAL MEDICINE

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## TYPE-SPECIFIC ANTIBODIES IN THE BLOOD OF PATIENTS WITH PNEUMOCOCCIC PNEUMONIA

DETECTION, INCIDENCE, PROGNOSTIC SIGNIFICANCE AND  
RELATION TO THERAPIES

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Because it was thought that a study of the demonstrable phenomena of immunity of the host which accompany recovery from pneumococcic infections provided an approach to rational therapeutic procedure, such phenomena were the chief concern of investigators prior to the introduction of sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine). Ever since the drug has been therapeutically employed attention has shifted to the infecting organism and emphasis has been placed on the mechanism of bacteriostasis. At present, attention is again directed to the humoral recovery mechanisms in relation to the action of sulfanilamide and its derivatives. Whitby found that sulfapyridine did not affect the quality, quantity or speed of production of antibodies. It has been observed that many patients who recover from pneumococcic pneumonia under treatment with sulfapyridine do so without any detectable circulating antibodies having developed. Results of adequate investigation of the possible complementary activity of the drug and of the antibody have not been recorded.

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From the medical service, Harlem Hospital, the Department of Hospitals of New York City, and the Littauer Pneumonia Research Fund of New York University College of Medicine.

This study received additional financial support from the Metropolitan Life Insurance Company and from Mr. Bernard M. Baruch, Mr. Bernard M. Baruch Jr., Miss Belle N. Baruch and Mrs. Robert H. Samstag.

There is still an appreciable mortality in all reported series of cases of pneumococcic pneumonia treated with sulfapyridine alone, although it appears to be less than the mortality previously experienced when treatment was with specific antipneumococcus serum. Whether the residual mortality might be diminished by therapy with a judicious combination of specific serum and sulfapyridine would appear to be answerable only by complete studies on large comparable groups of patients treated with sulfapyridine with and without serum. Such groups are not comparable without immunologic studies. During our observations on the antigen-antibody balance of patients with pneumococcic pneumonia who received treatment we compared the antibody response of 135 of them given sulfapyridine, serum or the two combined. Analysis of the results of such therapy forms the basis of the present communication, the incidence and significance of circulating capsular polysaccharide having been separately reported.

#### MATERIAL AND METHODS

The samples of blood were obtained from the 135 patients by the method indicated in the previous report.<sup>1</sup> Agglutinin and precipitin titers were simultaneously determined in all instances.

*Detection of Agglutinin.*—Five-tenths cubic centimeter of each of a series of dilutions (from 1:2 to 1:32) of patient's serum in physiologic solution of sodium chloride was mixed with 0.5 cc. of heat-killed pneumococci suspended in a similar solution. The bacterial suspension was freshly prepared by suspending the sediment of an eighteen hour serum-broth culture of a stock strain of pneumococci in physiologic solution of sodium chloride and adjusting the mixture to a ground glass density. The suspended organisms were heat killed (forty-five minutes at a temperature of 56 C.) before use. A positive and a negative control tube were included with each determination.

*Detection of Precipitin.*—Five-tenths cubic centimeter of each of a series of dilutions (from 1:2 to 1:8) of patient's serum in physiologic solution of sodium chloride was mixed with 0.5 cc. of the "optimal" dilution of a commercial preparation of homologous capsular polysaccharide in a physiologic solution of sodium chloride. A negative control containing 0.5 cc. of a 1:2 dilution of patient's serum and 0.5 cc. of the optimal solution of heterologous capsular polysaccharide was always included.

The determinations of antibodies were made at the same time as those of capsular polysaccharide elsewhere described.<sup>1</sup> In figure 1 of the preceding report a schematic representation of the method was given. All determinations were carried out in 10 by 75 mm. pyrex agglutination tubes and included centrifugation for thirty minutes at 2,000 revolutions per minute.

#### RESULTS

*Treatment with Sulfapyridine Alone.*—Sixty-five of the 135 patients in this series were treated with sulfapyridine alone. Generally an initial

---

1. Bukantz, S. C.; de Gara, P. F., and Bullowa, J. G. M.: Capsular Polysaccharide in the Blood of Patients with Pneumococcic Pneumonia: Detection, Incidence, Prognostic Significance and Relation to Therapies, Arch. Int. Med., February 1942.

oral dose of 5 Gm. was followed by a dose of 1 Gm. every four hours; occasionally supplementary intravenous injections of the sodium salt of the drug were given. The level of sulfapyridine in the blood was of the usual magnitude (2 to 8 mg. per hundred cubic centimeters).

A total of 350 specimens of blood were analyzed for antibodies (agglutinins and precipitins) during observation of the 65 patients treated with sulfapyridine alone. The 25 patients with type III pneumococcus pneumonia were studied most intensely and for each of 4 of them as many as 11 to 21 determinations were made.

TABLE 1.—*Incidence of Antibodies in Sixty-Five Sulfapyridine-Treated Patients with Pneumococcic Pneumonia*

	Number of Patients	Percentage of Patients
Total.....	65	100.0
Antibodies present.....	45	69.2
Agglutinins only.....	23	35.4
Agglutinins and precipitins.....	22	33.8
Precipitins only.....	0	0.0
No antibodies.....	20	30.7

TABLE 2.—*Day of Disease on Which Antibodies First Appeared in Forty-Five Sulfapyridine-Treated Patients with Pneumococcic Pneumonia*

Day of Disease	Number of Patients	Percentage of Patients	Number of Deaths
1 and 2.....	0	0	0
3.....	2	4.5	0
4.....	1	2.2	0
5.....	1	2.2	0
6.....	3	6.7	0
7.....	2	4.5	0
8.....	8	17.8	0
9.....	11	24.4	1
10+.....	17	37.8	2
Total.....	45	100.0	3

As recorded in table 1, either agglutinins or agglutinins and precipitins developed in 45, or 69.2 per cent, of the 65 patients at some time during the course of their illness. Precipitins were detected in approximately 50 per cent (22 to 45) of the patients in whom antibodies developed.

Table 2 gives the day of disease on which antibodies were first detected in the 45 patients. In 36, or 80 per cent, of them antibodies appeared first on or after the eighth day of disease. This observation is in agreement with those of Finland, Spring and Lowell<sup>2</sup> and of

2. Finland, M.; Spring, W. C., Jr., and Lowell, F. C.: Immunological Studies on Patients with Pneumococcic Pneumonia Treated with Sulfapyridine, *J. Clin. Investigation* 19:179, 1940.



Kneeland and Mulliken.<sup>3</sup> It will be noted from table 1 that both agglutinins and precipitins developed in 22 patients.

In 13 of them the agglutinin and the precipitin reactions became positive on the same day of disease, while in 8 a positive agglutinin reaction was obtained some time before the precipitin was detected; in 5 of these 8 patients the agglutinin reaction was positive four or more days earlier. In 1 patient with pneumonia caused by a type VII pneumococcus the precipitin reaction was repeatedly positive for eleven days before an agglutinin reaction was obtained. Subsequently, however, in

TABLE 3.—*Relation of Type of Causative Pneumococcus, Occurrence of Bacteremia, Age of Patient, Development of Antibodies and Outcome of Illness in Sixty-Five Sulfapyridine-Treated Patients with Pneumococcal Pneumonia*

Type	All Ages				40 Years or Less				40 Years or More			
	Total Number		Number with Antibodies		Total Number		Number with Antibodies		Total Number		Number with Antibodies	
	Pa-tients	Deaths	Pa-tients	Deaths	Pa-tients	Deaths	Pa-tients	Deaths	Pa-tients	Deaths	Pa-tients	Deaths
I	11 2*	1 0*	8 1*	0 0*	8 1*	0 0*	6 0*	0 0*	3 1*	1 0*	2 1*	0 0*
II	1 0*	0	1 0*	0	0		0		1 0*	0	1 0*	0
III	25 5*	4 2*	14 2*	1 1*	6 0*	0	4 0*	0	19 5*	4 2*	10 2*	1 1*
V	5 2*	1 1*	2 1*	1 1*	4 1*	1 1*	2 1*	1 1*	1 1*	0 0*	0	
VII	16 4*	1 1*	15 4*	1 1*	8 1*	0 0*	7 1*	0 0*	8 3*	1 1*	8 3*	1 1*
VIII	7 1*	1 1*	5 0*	0	3 0*	0	3 0*	0	4 1*	1 1*	2 0*	0
Total	65 14*	8 5*	45 8*	3 3*	29 3*	1 1*	22 2*	1 1*	36 11*	7 4*	23 6*	2 2*

\* Bacteremia.

the same patient the precipitin reaction became negative, while the agglutinin titer rose and persisted at a high level for at least thirteen days.

Table 3 gives the antibody response in relation to the type of infecting pneumococcus, age, presence of bacteremia, detectability of capsular polysaccharide and outcome for all 65 patients. Although the group is too small to permit generalization, there appears to be a tendency to a lower incidence of detectable antibodies among patients with type III pneumococcus pneumonia than among those whose pneumonia is caused by *Pneumococcus* type I, VII or VIII.

3. Kneeland, Y., Jr., and Mulliken, B.: Antibody Formation in Cases of Lobar Pneumonia Treated with Sulfapyridine, *J. Clin. Investigation* **19**:307, 1940.

Twenty-nine of the 65 patients were under 40 years of age; in 22 of them antibodies developed (76 per cent) (tables 3 and 4). Thirty-six patients were more than 40 years of age; in 23 of them (64 per cent) antibodies developed. Fifty-seven of the 65 sulfapyridine-treated patients recovered. In 15 of the 57 antibodies were not detected at any time. Of the 8 patients who died 1 each had pneumonia caused by

TABLE 4.—*Age of Patient and Outcome of Illness in Relation to Development of Antibodies in Sixty-Five Sulfapyridine-Treated Patients with Pneumococcic Pneumonia\**

Age	Total Number			Number with Agglutinins			Number with Agglutinins and Precipitins			Number Without Antibodies		
	Pa-tients	Deaths		Pa-tients	Deaths		Pa-tients	Deaths		Pa-tients	Deaths	
		No.	%		No.	%		No.	%		No.	%
Under 40 years.....	29	1	3.4	14	1	7.1	8	0	0.0	7	0	0.0
Over 40 years.....	36	7	19.5	9	2	22.2	14	0	0.0	13	5	38.4
Total.....	65	8	12.3	23	3	13.1	22	0	0.0	20	5	25.0

\* No significant differences in chi square exist between the mortality rates in the different groups.

TABLE 5.—*Relation of Occurrence of Bacteremia, Production of Capsular Polysaccharide, Development of Antibodies and Outcome of Illness in Sixty-Five Sulfapyridine-Treated Patients with Pneumococcic Pneumonia*

	Bacteremia Absent		Bacteremia Present		Total	
	Number of Patients	Number with Antibodies	Number of Patients	Number with Antibodies	Number of Patients	Number with Antibodies
Capsular polysaccharide present						
Patients.....	3	0	7	3	10	3
Deaths.....	2	0	4	2	6	2
Capsular polysaccharide absent						
Patients.....	48	37	7	5	55	42
Deaths.....	1	0	1	1	2	1
Total						
Patients.....	51	37	14	8	65	45
Deaths.....	3	0	5	3	8	3

pneumococcus type I, V, VII or VIII and in 4 the infecting pneumococcus was type III. Seven of the 8 patients were over 40 years of age; in 5 of them no antibodies were detected. In the remaining 3 patients who died only an agglutinin reaction was obtained. There were no deaths among the 22 patients who gave positive reactions for both precipitins and agglutinins.

Table 5 relates the incidence of bacteremia, the development of antibodies, the occurrence of capsular polysaccharide and the outcome of illness in the patients treated with sulfapyridine alone. It will be noted that of the 51 nonbacteremic patients, antibodies developed in 37

(72.5 per cent), in none of 3 who gave positive reactions for capsular polysaccharide and in 37 of 48 with negative reactions for that substance. In only 3 of 7 bacteremic patients were antibodies and polysaccharide present simultaneously, while antibodies developed in 5 of 7 bacteremic patients with negative reactions for the polysaccharide. Agglutinins only were detectable in 3 of a total of 10 patients with positive reactions for capsular polysaccharide, whereas either agglutinins alone or both agglutinins and precipitins developed in 42 of 55 patients who gave negative reactions for that substance. No deaths occurred among the 37 nonbacteremic patients with a negative reaction for capsular polysac-

TABLE 6.—*Highest Agglutinin and Precipitin Titers Observed Among Forty-Five Sulfapyridine-Treated Patients with Pneumococcic Pneumonia (Forty-Two Recoveries; Three Deaths) \**

	Total	Agglutinin		Precipitin		
		Dilution of Patient's Serum				
		1:16 or Less	1:32 or 1:64	$\frac{1}{4}$	$\frac{1}{8}$	$\frac{1}{16}$
		No. of Patients		No. of Patients		
Bacteremia and capsular polysaccharide absent.....	16†	13	3	0	0	0
	21‡	4	17	4	7	10
Bacteremia and capsular polysaccharide present.....	3	2 (1)§	1 (1)#	0	0	0
Bacteremia present and capsular poly- saccharide absent.....	4†	3 (1)	1	0	0	0
	1‡	1	0	1	0	0
Total.....	45	23	22	5	7	10

\* All patients in whom antibodies developed before the eighth day of illness recovered.

† Agglutinin only.

‡ Both agglutinin and precipitin.

§ The figure in parentheses indicate the number of deaths in the group.

# The case of this patient is described in the text and in a previous paper.<sup>1</sup>

charide in whom antibodies developed, but there were 3 deaths among 14 such patients in whom antibodies failed to develop. Among the bacteremic patients, 3 of the 8 with antibodies and 2 of the 6 without antibodies died. Among the 7 bacteremic patients with positive reactions for capsular polysaccharide, 2 of the 3 in whom antibodies developed died and 2 of the 4 in whom antibodies did not develop died. The 3 remaining patients with such reactions were all nonbacteremic, and none showed antibodies; 2 of them died. Antibodies developed in 5 of 7 bacteremic patients whose reaction for the polysaccharide was negative, and 1 of the 5 died.

From table 6 it will be noted that only agglutinins developed in 16 nonbacteremic patients with a negative reaction for capsular polysaccharide; in 13 of them the agglutinin titer ranged between 1:4 and 1:16. In 21 such patients both agglutinins and precipitins developed, and in 17 the agglutinin titer was 1:32 or greater. As just noted, none of

these patients died. Of 5 patients whose agglutinin titer was 1:32 or more but in whom precipitins did not develop, 1 died. This patient was a 54 year old diabetic woman with bacteremia and a positive reaction for capsular polysaccharide who was admitted to the hospital late in the course of her illness with evidences of accumulation of fluid in the pleural cavity; her blood was examined on only one occasion. Her death was at least partly determined by the severity of the diabetes, the presence of capsular polysaccharide and apparently a too early cessation of treatment with sulfapyridine. Three recoveries occurred among 5 bacteremic patients (2 with positive and 3 with negative reactions for capsular polysaccharide) in whom precipitins failed to develop and whose agglutinin titer was 1:16 or less. Recovery occurred in all 13 non-bacteremic patients in whom the agglutinin titer was 1:16 or less and yet in whom no precipitins were detectable.

TABLE 7.—*Distribution of Positive Antibody Responses and Outcome of Illness in Relation to Day of Disease on Which Sulfapyridine Therapy Was Begun in Sixty-Five Patients with Pneumococcic Pneumonia Treated with Sulfapyridine Alone*

Day of Disease	Patients	Total		Number of Patients with Antibodies
		Deaths		
		Number	Percentage	
First to fourth.....	26	3	11.6	18
Later than fourth.....	39	5	12.8	27

Table 7 shows the relation between the day of disease on which treatment with sulfapyridine alone was begun, the antibody response and the outcome of the disease. Sixty per cent of the 65 patients given only sulfapyridine were first treated on or after the fifth day, and the percentage of positive antibody responses and the mortality rate were identical for those treated "early" and for those treated "late."

*Treatment with Specific Antipneumococcus Serum Alone.*—Thirty-one patients were treated with varying amounts of specific antipneumococcus serum (horse or rabbit) alone. Antibodies were detected in the blood of all 31 and always were found in the first sample of blood tested after therapy was begun. Agglutinins and precipitins were present in 27 patients, of whom 2 died. In 3 patients agglutinins only were detected and these in relatively low titer, 1:8; all 3 recovered. In the remaining patient on the eleventh day of a type IV pneumococcus pneumonia which had been treated on the second day precipitins only were detected; the illness terminated in subacute bacterial endocarditis due to the same organism.

The total dose of serum administered ranged from 85,000 to 1,239,000 U. S. P. units. The antibody titers reached were appreciably higher for these patients than for those treated with sulfapyridine alone. In 24 of the 30 patients in whom agglutinin was present the titer was 1:32 or greater, in 3 it was 1:16 and in the remaining 3 it was 1:8. Of the 28 patients with a positive precipitin reaction, the titer was 1:8 or greater in 25 (greater than 1:16 in 8) and 1:4 in the remaining 3. Table 8 summarizes by type of causative pneumococcus the relation between age and outcome in this group of patients. Those with type III

TABLE 8.—*Relation of Type of Causative Pneumococcus, Incidence of Bacteremia, Age of Patient, Presence of Capsular Polysaccharide and Outcome of Illness in Thirty-One Patients with Pneumococcal Pneumonia Treated with Antipneumococcus Serum Alone*

Type	All Ages		40 Years or Less		40 Years or Over	
	Patients	Deaths	Patients	Deaths	Patients	Deaths
I.....	11 2*	0 0*	9 1*	0 0*	2 1*	0 0*
II.....	1 1*	0 0*	0	..	1 1*	0 0*
III.....	2 (1)† 0*	2 (1) 0*	1 (1) 0*	1 (1) ..	1 0*	1 ..
IV.....	1 1*	1 1*	0	..	1 1*	1 1*
V.....	2 1*	0 0*	2 1*	0 0*	0	..
VII.....	9 4*	0 0*	5 2*	0 0*	4 2*	0 0*
VIII.....	5 1*	0 0*	4 1*	0 0*	1 0*	0
Total.....	31 (1) 10*	3 (1) 1*	21 (1) 5*	1 (1) 0*	10 5*	2 1*

\* Bacteremia.

† The figure in parentheses indicates the number of patients in whose blood capsular polysaccharide was detectable.

pneumococcus pneumonia were usually alternated for treatment with sulfapyridine alone and with specific serum combined with sulfapyridine, which accounts for the fact that so few (2) patients received only serum.

*Treatment with Sulfapyridine and Specific Antipneumococcus Serum.*—Thirty-nine patients were treated with both specific antipneumococcus serum and sulfapyridine. Antibodies were not detected in 3 of them. These were 3 of the 13 patients with type III pneumococcus pneumonia who were thus treated; all 3 were nonbacteremic, and their blood gave a negative reaction for capsular polysaccharide; all of them recovered. In 6 patients only agglutinins were detected (1 case each of types II, III, V and VIII pneumococcus pneumonia and 2 cases of type I pneumococcus pneumonia); in 3 of these the titer was 1:16 or less, and in the

remaining 3, 1:32 or greater. These 6 patients also recovered. In 27 patients both agglutinins and precipitins were detected. The agglutinin titer was 1:16 or less in 8 patients and 1:32 or greater in 19, while the precipitin titer was 1:4 in 7 and 1:8 or greater in 20 (13 gave a 1:16 titer). Five of these patients died; in 3 of the 5 the agglutinin titer was greater than 1:32 and the precipitin titer greater than 1:8. There were neither complications of the pneumonia nor evidence of other significant disease in these patients. In 3 of them capsular polysaccharide was found; their cases are described in the preceding paper (cases 5, 8

TABLE 9.—*Relation of Type of Causative Pneumococcus, Incidence of Bacteremia, Age of Patient, Presence of Capsular Polysaccharide and Outcome of Illness in Thirty-Nine Patients with Pneumococcic Pneumonia Treated with Both Sulfapyridine and Antipneumococcus Serum*

Type	All Ages		40 Years or Less		40 Years or Over	
	Patients	Deaths	Patients	Deaths	Patients	Deaths
I.....	10 1*	0 0*	5 1*	0 0*	5 0*	0
II.....	2 1*	0 0*	1 1*	0 0*	1 0*	0
III.....	13 (2)† 2*(1)	2 (2) 1*(1)	5 1*	0 0*	8 (2) 1*(1)	2 (2) 1*(1)
V.....	2 0*	1 ..	1 0*	1 ..	1 0*	0
VII.....	8 (2) 2*(1)	2 (1) 2*(1)	4 0*	0 ..	4 (2) 2*(1)	2 (1) 2*(1)
VIII.....	4 (1) 1*(1)	0 0*	1 0*	0	3 (1) 1*(1)	0 0*
Total.....	39 (5) 7*(3)	5 (3) 3*(2)	17 3*	1 0*	22 (5) 4*(3)	4 (3) 3*(2)

\* Bacteremia.

† The figure in parentheses indicates the number of patients in whose blood capsular polysaccharide was detectable.

and 14).<sup>1</sup> In 1 of them moderate leukopenia developed during the course of treatment but subsided promptly after therapy with sulfapyridine was stopped (case 5). To 1 of the other patients antipneumococcus serum (type V) was given on the fifth day of illness and sulfapyridine on the sixth day, and to the remaining 1 patient serum (type VII) and sulfapyridine were given on the twelfth day. In the case of the last 2 patients complete antibody studies were not possible. Table 9 summarizes the incidence of the various types of pneumococcic pneumonia and the relation between age and outcome in patients treated with both serum and sulfapyridine.

The total dose of serum administered to these patients ranged from 12,500 to 2,525,000 U. S. P. units. There was no significant difference in the antibody titers developed in the patients receiving serum alone

and those in patients given serum and sulfapyridine simultaneously. In some instances high titers were obtained despite administration of relatively small quantities of serum, while administration of larger

TABLE 10.—*Relation of Antibody Response, Day of Disease on Which Therapy Began, Amount of Antipneumococcus Serum Administered and Type of Causative Pneumococcus in Thirty-Four Patients with Pneumococcic Pneumonia Treated with Serum Alone*

Case No.	Type of Pneumococcus	Units (U. S. P.) of Serum	Day of Disease Serum Therapy Began	Highest Titers							
				Agglutinins					Precipitins		
				4	8	16	32	64+	4	8	16+
1	II	1,239,000	8	..	..	..	1	..	..	..	1
2	I*	525,000	5	..	..	..	..	1	..	..	1
3	I	280,250	2	..	..	..	..	1	..	..	1
4	I	210,000	4	..	..	1	..	..	1	..	..
5	I	160,000	7	..	..	..	..	1	..	..	1
6	I	165,000	2	..	1	..	..	..	0	0	0
7	III*	700,000	1	..	..	1	..	..	1	..	..
8	III	260,000	?	..	..	..	..	1	..	..	1
9	IV*	733,000	4	0	0	0	0	0	..	..	1
10	V*	634,000	6	..	..	..	..	1	..	..	1
11	V	140,000	5	..	..	..	1	..	..	1	..
12	VII	320,000	2	..	..	..	..	1	..	..	1
13	VII*	640,000	7	..	..	..	..	1	..	..	1
14	VII	259,000	4	..	1	..	..	..	0	0	0
15	VIII	85,000	4	..	1	..	..	..	0	0	0
16	VIII*	286,000	5	..	..	..	..	1	..	..	1
17	VIII	184,000	3	..	..	..	1	..	..	..	1
18	I*	235,000	3	..	..	..	1	..	0	0	0
19	I	12,500	5	1	..	..	..	..	0	0	0
20	I	98,000	4	..	..	..	..	1	..	..	1
21	II	120,000	4	..	..	1	..	..	0	0	0
22	III	123,500	7	..	1	..	..	..	0	0	0
23	III	84,500	5	..	..	..	..	1	..	..	1
24	III	170,000	2	0	0	0	0	0	0	0	0
25	III	300,000	2	0	0	0	0	0	0	0	0
26	III	200,000	2	0	0	0	0	0	0	0	0
27	III*	495,000	12	..	..	1	..	..	..	1	..
28	V	273,000	5	1	..	..	..	..	1	..	..
29	V	200,000	8	..	..	..	1	..	0	0	0
30	VII*	2,525,000	2	..	..	..	1	..	..	1	..
31	VII*	160,000	12	..	..	..	..	1	..	..	1
32	VII	192,000	5	..	..	..	..	1	..	1	..
33	VIII*	180,000	1	..	..	..	..	1	..	..	1
34	VIII	132,000	3	..	..	..	..	1	0	0	0
No antibodies.....				3							
Agglutinins only.....					9						
Precipitins only.....						1					
Agglutinins and precipitins.....							21				

\* Bacteremia.

quantities did not always result in high antibody titers. As has just been noted, the development of a high titer of antibody was not always followed by recovery. The relation of antibody response to the quantity of serum administered, with the type of infecting pneumococcus and the day of disease on which administration of serum was begun, is given in table 10 for some of the patients.

## COMMENT

Detectable antibodies developed during recovery in a high percentage (70) of the patients treated with sulfapyridine alone, though they appeared in the majority some days after the disease seemed to be under clinical control. These observations are in agreement with those of Finland, Spring and Lowell,<sup>2</sup> who found that antibodies developed in sulfapyridine-treated patients with about the same frequency as in untreated patients. Kneeland and Mulliken,<sup>3</sup> however, found a considerably lower incidence of antibody response among sulfapyridine-treated patients with lobar pneumonia (4 of 19) and suggested that the low rate of and delay in antibody formation might be a consequence of lessened stimulus resulting from the action of the drug on the invading organism. Kneeland and Mulliken performed only the precipitin test on the assumption that agglutinins, precipitins and protective antibodies are the same and therefore are detectable with equal ease. While the various phenomena of immunity may be manifestations of a single antibody, the physical conditions required for qualitative detection are quite different. This difference is indicated by the detectability of protective antibodies earlier than agglutinins in an appreciable percentage of the cases reported by Finland and his associates<sup>2</sup> and the detectability of agglutinins without precipitins in a large number of our sulfapyridine-treated patients. Tillett and Francis<sup>4</sup> stated that "type specific antibodies were more easily demonstrable by agglutination tests with the intact type specific cells," although in most of their 19 horse-serum-treated patients agglutinins and precipitins became detectable at the same time.

Of the 45 patients in our sulfapyridine-treated group in whom antibodies developed, 3 died and 42, or 93.4 per cent, recovered. Of the 20 sulfapyridine-treated patients in whom antibodies failed to develop, 5 died and 15, or 75 per cent, recovered. Apparently, though not all the sulfapyridine-treated patients die if antibodies fail to develop, the appearance of antibodies is not always followed by recovery.<sup>5</sup> The fatality rate among patients in whom antibodies developed was only one quarter of the rate among those in whom they failed to develop. For this reason it is important to determine the factors involved in the production of antibodies.

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4. Tillett, W. S., and Francis, T., Jr.: Cutaneous Reactions to Polysaccharides and Proteins of the Pneumococcus in Lobar Pneumonia, *J. Exper. Med.* **50**: 687, 1929.

5. While this paper was in press, a study by E. C. Curnen and C. M. MacLeod (The Effect of Sulfapyridine upon the Development of Immunity to Pneumococcus in Rabbits, *J. Exper. Med.* **75**:77, 1942) appeared. Their data support the view that effective therapy of pneumococcic infections in man with sulfanilamide compounds is associated with the development of active immunity.



The rate of production of antibodies was least among those patients in whom capsular polysaccharide was detected, and it is to be expected that production will be lowest among patients whose infection is due to a type of pneumococcus which produces large amounts of capsular polysaccharide. This is particularly important in infections caused by *Pneumococcus* type III. The appearance of capsular polysaccharide in infection caused by any type of pneumococcus is conditioned by the duration of the disease before successful therapy is begun. In our series, the incidence of patients with a positive reaction for capsular polysaccharide was equal among those treated before and those treated after the fourth day of illness. However, the great majority of patients in the earlier treated series entered the hospital on either the third or the fourth day of their disease and, in effect, created a series almost entirely composed of late treated patients. It is probable that the incidence of capsular polysaccharide would be considerably lower in a series of patients treated early in their disease. And in such patients we should expect to find an even higher incidence of antibody response. Likewise, a low antibody response was observed among older patients and among those with bacteremia.

Because fatality rates of sulfapyridine-treated patients are greater when antibodies fail to appear, we believe it advisable to administer specific serum to those patients in whom a failure of antibody formation is most likely to occur, i. e., those with infections caused by *Pneumococcus* type III, those with bacteraemia or a positive reaction for capsular polysaccharide, those over 40 and those treated late in the course of their disease.

The effort to analyze the deaths among serum-treated patients in terms of quantitative antibody response met with little success. In our relatively small group of patients treated with both sulfapyridine and serum fatalities occurred despite attainment of a high antibody titer. In contrast to this is the observation that of the sulfapyridine-treated patients, there was uniform recovery among those in whom the greatest antibody response developed (i. e., precipitins as well as agglutinins). When antibodies develop spontaneously, as in sulfapyridine-treated patients, such antibodies are immunologically uniform with the stimulating antigen, i. e., the invading organism with its particular capsular polysaccharide. Either other responses (cellular) have been stimulated during the production of antibodies or the passively introduced antibody may imperfectly fit the antigen, and this may account for the discrepancy in outcome of illness in drug-treated and in serum-treated patients having a high antibody titer. It is evident that information concerning the quantitative and the qualitative significance of the antibodies in serum-treated patients is at present inadequate.

## SUMMARY

Repeated agglutinin and precipitin determinations were made on 135 patients with type I, II, III, IV, V, VII or VIII pneumococcus pneumonia during the course of treatment with sulfapyridine or specific serum or the two in combination.

Sixty-five patients received sulfapyridine alone; antibodies developed in 45 of them. Agglutinins alone were found in 23 patients; agglutinins and precipitins, in 22. Five of the 20 patients without antibodies died, a mortality rate of 25 per cent. It is apparent that the development of a positive antibody response is associated with a higher recovery rate. Of the 27 patients with the greatest amount of spontaneously produced antibody per unit volume of blood (i. e., agglutinin titer of 1:32 or greater and/or circulating precipitin) only 1, or 3.7 per cent, died. Of the patients having agglutinins of low titer and no precipitins 2 died. Finally, 22 of the 27 patients gave a reaction for both precipitins and agglutinins. None of them died.

In 36 (80 per cent) of the 45 patients in whom antibodies developed, they were first detected on the eighth day of disease or later.

The incidence of detectable antibodies was slightly lower among patients with type III pneumococcus pneumonia than among those whose infection was caused by *Pneumococcus* type I, VII or VIII. The antibody response was definitely lower in patients over 40.

The incidence of positive antibody response was slightly higher in the nonbacteremic than in the bacteremic patients. The lowest incidence of positive antibody responses occurred among the 10 patients with a positive reaction for capsular polysaccharide; antibodies (agglutinins only) developed in only 3 of the 10.

The incidence of positive antibody response and mortality rate was unchanged whether patients were treated in the early stages of the disease or in the late stages. However, in the case of the average early treated patient therapy was begun on the third or fourth day of disease.

Thirty-one patients were treated with specific antipneumococcus serum alone; antibodies were detected in all of them in the first sample of blood obtained after therapy was begun. Three of them died.

Thirty-nine patients received both specific serum and sulfapyridine. Antibodies failed to develop in 3 of them, all with infection caused by type III *Pneumococcus* and none with bacteremia, despite administration of 170 to 300,000 units of serum. All 3 patients, however, recovered. Among 27 of the 39 patients who gave positive precipitin and agglutinin reactions, 5 deaths occurred. Four of the patients who died had either bacteremia or a positive reaction for capsular polysaccharide or both. The fifth patient had neither bacteremia nor a positive reaction for capsular polysaccharide and had only low agglutinin and precipitin titers.

No constant relation was observed between the amount of serum administered and the height of the antibody response either in the patients treated with serum alone or in those treated with serum and sulfapyridine in combination.

It is suggested that specific serum therapy be employed with sulfapyridine therapy whenever there are circumstances which may impede the spontaneous production of antibody, i. e., age over 40 years, presence of bacteremia or circulating capsular polysaccharide or presence of infection caused by *Pneumococcus* type III.

Miss Ruth Mayer assisted in titrations of capsular polysaccharide and of antibodies on most of the patients.

Miss Constance Lehair and Miss Evelyn Greenbaum assisted in the preparation of the manuscript.

# EFFECT OF ESTROGEN ON THE UTILIZATION OF THE VITAMIN B COMPLEX

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In previously recorded clinical observations<sup>1</sup> we have reported evidence indicating an interrelation between hormones of the anterior lobe of the pituitary and the utilization of the vitamin B complex. In a number of instances, pellagra refractive to vitamin therapy was cured or improved by the parenteral administration of the whole extract of the anterior lobe of the pituitary or of an anterior pituitary extract containing the growth-stimulating or gonadotropic factor.<sup>2</sup> The evaluation of the effects of the growth-stimulating or gonadotropic substance is somewhat vitiated by the inability to exclude the possibility that other factors are present in the solutions administered. The possible effect of any vitamin B complex in these extracts is remote when considered in relation to the amounts of vitamin B complex previously administered.

The effect of the anterior lobe of the pituitary on the utilization of the vitamin B complex may be the result of the action of (a) one or more of the known hormones, (b) another gland of internal secretion as influenced by a pituitary hormone or (c) a pituitary hormone as yet unknown.

One approach to the problem is to ascertain the effects of various glandular substances on vitamin B complex deficiency. For example, Sydenstricker<sup>3</sup> has observed the healing of "lesions of ariboflavinosis"

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1. (a) Sutton, D. C., and Ashworth, J.: Cachexia Responding to Extract of the Anterior Lobe of the Pituitary Gland, *J. Lab. & Clin. Med.* **25**:848, 1940; (b) The Interrelation Between the Vitamin B Complex and the Anterior Lobe of the Pituitary Gland, *ibid.* **25**:1188-1192, 1940; (c) in Harris, S., and Harris, S., Jr.: *Clinical Pellagra*, St. Louis, C. V. Mosby Company, 1940, sect. 4, chap. 17. (d) Sutton, D. C.: Interrelation Between Vitamin B Complex and the Anterior Lobe of the Pituitary Gland, *South. M. J.* **34**:47-51, 1940.

2. The extracts of the anterior lobe of the pituitary were furnished by Armour and Company, Chicago.

3. Sydenstricker, V. P.: Personal communication to the authors.

after the administration of desoxycorticosterone to a patient with Addison's disease.

This paper records the observations made on the effect of estrogens on patients who, because of chronic alcoholism, evidence of hepatic cirrhosis or slight lesions of the skin, mucous membrane or the nervous system, were classified by us as having subclinical pellagra.

Diethylstilbestrol was used at the beginning of the study; it was later replaced by  $\alpha$ -estradiol dipropionate<sup>4</sup> because the latter is considered to be a natural estrogen in contradistinction to the synthetic substance diethylstilbestrol. Permission for this type of management was obtained from each patient. The effects of these estrogens on the utilization of the vitamin B complex, or rather on the condition of the patient, is best illustrated by the following case reports. All patients received the general full diet of the hospital, which is known to be adequate in regard to essential food factors.

#### REPORT OF CASES

CASE 1.—J. C., a 48 year old white man, entered the Cook County Hospital on Dec. 13, 1940, complaining of diarrhea, cutaneous rash and precordial pain of three weeks' duration. He had been chronically addicted to alcohol for many years, drinking an average of 1 quart (946 cc.) of whisky daily. During November he had had a severe infection of the upper respiratory tract, accompanied by diarrhea, with fifteen to twenty stools daily. On entrance he still was having five to six stools daily. Neither blood nor amebas were found in the feces. Shortly after the onset of diarrhea the patient had noticed a generalized rash, which caused some pruritis. The day before entering the hospital he experienced severe "shooting" pains in the arms and legs. He had had several similar attacks on previous occasions.

Physical examination revealed nothing abnormal except a maculopapular rash on the forearms and the anterior surface of the body.

The patient was allowed a full diet. From December 13 to December 27 he was given daily 25 mg. of thiamine hydrochloride intravenously and 450 mg. of nicotinic acid orally.

The rash disappeared, and the peripheral pains were much improved. Slight scaling of the dorsum of the hands (pellagrous?) remained.

After medication with thiamine was stopped, on December 28, the patient was given 3 mg. of diethylstilbestrol daily until Feb. 6, 1941. On January 9 the cutaneous lesions on the anterior surfaces of the legs were exacerbated. On January 13 and 19 he was given 200 cc. of a 50 per cent solution of dextrose intravenously. No fever occurred. These injections were followed by a marked exacerbation of the cutaneous lesions, such as occurs in a case of pellagra after the intravenous administration of a solution of dextrose. At this time definite scaling at the angles of the mouth was observed, and the patient mentioned tenderness of the nasal mucosa. On February 4 he complained of an infection of the upper respiratory tract, with acute rhinitis and bronchitis. The pain in the legs became so severe that he was confined to bed. The diethylstilbestrol was discontinued

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4. Alpha-estradiol dipropionate (di-ovocilin) was furnished by the Ciba Pharmaceutical Products, Inc., Summit, N. J.



Case 1, Feb. 10, 1941. Note the red tongue and the scaling lesions at the corners of the mouth and along the lips and nose.



February 6, and instead 1 mg. of  $\alpha$ -estradiol dipropionate was given intramuscularly on each of the four succeeding days.

During the night of February 10 the patient was found on the hospital grounds, clad only in a short nightshirt. When examined the next day, he exhibited a severe psychosis. The marked scaling around the lips, especially at the angles of the mouth, extended up on the nasal septum. Similiar scaling was also present in the scrotal thigh folds. The tongue was fiery red. Red, painful, nonpitting edema of both hands completed the picture of pellagra without diarrhea. The daily administration of 100 mg. of nicotinic acid intravenously and 450 mg. orally and 8 cc. of liver extract <sup>4a</sup> intramuscularly caused rapid improvement.

This patient had definite, though mild, pellagra when he entered the ward and had had previous attacks due to vitamin B complex deficiency, as evidenced by attacks of peripheral pain (peripheral neuritis). He was given dextrose intravenously on January 13 and 19 because we believe that the acute exacerbation which follows its use in cases of pellagra serves to confirm the diagnosis of the condition. The extreme severity of the symptoms by February 10 would appear to be the result of the infection of the upper respiratory tract which began February 4. We have frequently noted the onset of pellagra or neuritis in persons chronically addicted to alcohol shortly after an infection of the upper respiratory tract.

CASE 2.—W. C., a 44 year old white man, was first seen in January 1939 by one of us (J. A.). He was chronically addicted to alcohol. In October 1938 he was told by his physician that he had cirrhosis of the liver. He stopped drinking and continued on a high carbohydrate diet as ordered. He enjoyed relatively good health until the Christmas holidays of 1939, when he drank heavily of sherry wine (but no distilled spirits) for several days.

When first seen the patient was acutely ill, with a temperature of 103.6 F., jaundice and marked ascites, which was relieved by paracentesis. After this episode of acute illness, severe, painful glossitis developed, which was relieved by frequent intramuscular injections of liver extract from January to September 1940.

After the administration of liver extract was stopped in September, the patient was given 6 mg. of stilbestrol orally for three successive days. On the fourth day he complained of severe glossitis and a painful nasal mucosa. Severe, scaly, seborrhoid lesions about the lips and nose and painful fissures in the angles of the mouth were observed. These lesions were relieved within ten days by the daily administration of 300 mg. of nicotinic acid orally and 4 cc. of liver extract intramuscularly. The patient died in November 1940 of a ruptured esophageal varix, after thirty-two paracenteses.

This man with severe hepatic damage had a type of glossitis frequently seen in cases of pellagra refractory to vitamin therapy, which is usually controlled by the parenteral administration of liver extract.

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4a. A crude aqueous extract from which the coagulable protein had been removed by heat was used. One cubic centimeter of this extract, which was prepared by the Armour and Company research laboratories, is equal to 12.5 Gm. of fresh liver.



During liver therapy there were intervals of ten days without treatment before the return of mild symptoms. After a dose of 24 mg. of diethylstilbestrol, severe glossitis developed and cheilosis of the mouth and nose appeared for the first time.

CASE 3.—E. S., a 49 year old white man, entered the Cook County Hospital Dec. 12, 1940, complaining of dyspnea of a year's duration, associated with occasional edema of the ankles, and severe pains in the legs and diarrhea, with twenty to twenty-four watery stools daily, of a week's duration. He was a bartender by occupation and had been a heavy drinker for many years.

He was well nourished and had a blood pressure of 160 systolic and 80 diastolic and slight icterus. The liver and spleen were palpable and firm; more than moderate ascites was present. A diagnosis of alcoholic cirrhosis of the liver was made.

From Dec. 12, 1940, to Jan. 11, 1941 50 mg. of thiamine hydrochloride was given intravenously each day; this therapy was followed by almost complete recovery from polyneuritis. From January 11 until February 4 3 mg. of diethylstilbestrol was given orally each day. Beginning February 6, 1 mg. of  $\alpha$ -estradiol dipropionate was administered daily until February 10, when the dose was increased to 5 mg. daily. The administration of the thiamine hydrochloride was continued throughout. Slight scaling of the corners of the mouth was noticed a week after the administration of diethylstilbestrol. The nasal mucosa became painful, and numbness and paresthesias developed in the hands. The pains in the legs became less severe.

This patient also was chronically addicted to alcohol, with a damaged, cirrhotic liver. The only evidence of avitaminosis manifested on entrance to the hospital was polyneuritis of the legs. He was given thiamine hydrochloride until he was almost free from pain. While he was still taking thiamine, after having received 21 mg. of diethylstilbestrol within seven days, mild cheilosis appeared, the nasal mucosa became painful and numbness and paresthesias developed in the hands.

CASES 4 AND 5.—We have observed 2 patients, 1 with a carcinoma and the other with alcoholic cirrhosis of the liver, in whom scaling and seborrheic lesions about the lips occurred after the administration of diethylstilbestrol. However, both these patients left the hospital before our observations were completed.

In the following cases the symptoms of vitamin B complex deficiency occurred after the administration of estrogens in the absence of a known pathologic condition of the liver.

CASE 6.—Mrs. L. H., a 52 year old white woman, was first seen in October 1940, when she complained of menopausal symptoms, headaches and severe muscle pains in the arms and legs. A complete hysterectomy had been performed in 1925.

Her physical examination revealed nothing relevant other than a blood pressure which persisted at about 170 systolic and 100 diastolic.

Because of the menopausal symptoms, she was given 60,000 international units of estrogen in the form of estrons (theelin) during thirty days, without obvious improvement. During November 1940 she was given 3 mg. of diethylstilbestrol orally each day for four days, at which time severe nausea developed. Severe glossitis appeared, with fissures and scaling at the corners of the mouth. She also complained

of a painful nasal mucosa. These lesions persisted for three months, despite treatment with daily intramuscular injections of 2 cc. of liver extract.

This patient gave no evidence of vitamin deficiency before the administration of the estrogen. After receiving 60,000 units of estrogen (estrone) in thirty days, she was given 12 mg. of diethylstilbestrol within four days. After four days of medication with diethylstilbestrol, cheilosis and painful nasal mucosa developed. Nausea occurred at the same time and could hardly be the cause of an acute vitamin deficiency.

CASE 7.—T. R., a 28 year old white woman, unmarried, had for five years all the clinical manifestations of generalized scleroderma and extremely painful peripheral neuritis. Marked muscular atrophy was accompanied by limitation of motion in all joints. She had had amenorrhea, except for atypical menses, for two years.

The peripheral pains were almost completely relieved by intramuscular injections of liver extract.

In August 1940 the patient had an almost normal menstrual period, during which time she was nearly free from subjective symptoms. From August to September 26 she was given 1 mg. of diethylstilbestrol orally each day. On September 10 severe polydipsia and polyuria developed, which have persisted to the present time (March 1941). The level of blood sugar was normal, and no glycosuria had been observed.

On September 16 she complained of severe glossitis, painful fissures at the angles of the mouth, cheilotic lesions of the lips and a painful nasal mucosa. During this time she was free from pain, but the other symptoms continued until September 26, when the diethylstilbestrol was discontinued. She was given parenteral injections of 4 cc. of liver extract daily. After one week all lesions had completely disappeared.

This young woman probably had had a vitamin deficiency during the past five years, as evidenced by the relief of the peripheral neuritis by the intramuscular injection of liver extract.

#### COMMENT

Study of the literature reveals that the effect of estrogen observed in these cases is not entirely unexpected. We have previously noted the tendency to exacerbation of the symptoms of pellagra during the menstrual cycle.<sup>1b</sup> One of the early symptoms observed in all these patients was a tender and painful nasal mucosa. Mortimer, Wright and Collip<sup>5</sup> observed a cyclic change in the nasal mucosa of monkeys (*Macaca mulatta*) at intervals of about twenty-eight days, the peaks being chiefly at "premenstrual time." This response is produced in the intact animal by administration of crystalline estrone (theelin), estriol (theelol) and emmenin. The change is seen clearly in the middle and inferior conchae

5. Mortimer, H.; Wright, R. P., and Collip, J. B.: The Effect of the Administration of Oestrogenic Hormones on the Nasal Mucosa of the Monkey (*Macaca Mulatta*), *Canad. M. A. J.* 35:503-513 and 615-621, 1936.

as reddening and/or swelling of the mucosa. The effect is produced in immature and mature male and female animals and in female castrates.

The lesions noted in the mucous membrane of the mouth are possibly similar to those observed by Ziskin and Blackberg.<sup>6</sup> Castration of the female rhesus monkey causes alteration of the arrangement of the prickly cell layer of the alveolae gingivae and tissue degeneration, and hypophysectomy causes marked degenerative changes in gingival and oral mucous membranes. Castration of male rhesus monkeys causes changes in the gingival and oral mucous membranes resembling the effects of injection of estrogens namely, hyperkeratinization.

There is ample evidence that estrogens depress the activity of the anterior lobe of the pituitary or that they may cause actual anatomic changes if administered to excess. Cramer and Horning<sup>7</sup> observed that mice treated over a long period with estrone manifested a condition of cachexia similar to that seen in Simmonds' disease. At autopsy they found degenerative changes in the adrenal glands, hypertrophy of the islands of Langerhans and tumors (chromophobe adenomas) of the pituitary, as well as functional changes resembling those occurring after hypophysectomy.<sup>8</sup> Morphologically, hyperplasia of the anterior lobe occurs, in which, however, the number of chromophil cells is greatly diminished and the enlarged anterior lobe consists mainly of chromophobe cells. There is intense congestion of the anterior lobe, which may lead to hemorrhages, together with extensive production of colloid. Lacassagne<sup>9</sup> confirmed the report by Cramer and Horning. McEwen, Selye and Collip<sup>10</sup> observed adenoma of the pituitary both in male and in female rats given estrone over a long period.

In all but cases 6 and 7 a pathologic condition was known to be present in the liver. Sydenstricker<sup>11</sup> prepared an extract from the liver of a patient dying of uncomplicated pellagra and determined that the anti-pernicious-anemia factor was present. However, 2 patients with pellagra showed no response whatever when treated with this extract.

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6. Ziskin, D. E., and Blackberg, S. N.: Effect of Castration and Hypophysectomy on Gingival and Oral Mucous Membranes of Rhesus Monkeys, *J. Dent. Research* **19**:381-390, 1940.

7. Cramer, W., and Horning, E. S.: The Effect of Oestrin on the Pituitary Gland, *Lancet* **1**:247, 1936.

8. Cramer, W., and Horning, E. S.: Experimental Production by Oestrin of Pituitary Tumors with Hypopituitarism and Mammary Cancer, *Lancet* **1**:1056, 1936.

9. Lacassagne, A.: A Comparative Study of the Carcinogenic Action of Certain Oestrogenic Hormones, *Am. J. Cancer* **28**:735, 1936.

10. McEwen, C. S.; Selye, H., and Collip, J. B.: Some Effects of Prolonged Oestrin Administration in Rats, *Lancet* **1**:775, 1936.

11. Sydenstricker, V. P., in Harris, S., and Harris, S., Jr.: Clinical Pellagra, St. Louis, C. V. Mosby Company, 1940, chap. 16, p. 267.

Both responded later to a commercial liver extract. The presence of hepatic damage may interfere with the utilization and storage of the vitamin B complex or increase the requirement, as it does in the case of carotene (provitamin A), vitamin D and vitamin K. The administration of estrogens (estradiol is destroyed by the liver) may further increase the demand for vitamin B complex or may prevent its utilization directly by action on the tissue or indirectly by suppressing the activity of the anterior lobe of the pituitary.

In cases 1 and 3 (and cases 4 and 5, for which we mentioned the records were incomplete) the patients were given the full ward diet of the Cook County Hospital. Although the vitamin B complex value of this diet has not been accurately determined, it is sufficient to cause complete recovery of the polyneuritis and mild pellagra occurring in young persons addicted to alcohol.

The patients in cases 2, 6 and 7 were private patients on adequate diets generally considered to contain the ordinary requirement of vitamins. Nausea occurred only in case 6, and even in this case its duration was too short to have been an etiologic factor in vitamin deficiency.

In all cases reported, after administration of estrogenic substances, evidence of vitamin B complex deficiency appeared, namely, cheilotic lesions, or ariboflavinosis; glossitis, cutaneous lesions and psychosis, or nicotinic acid deficiency, and polyneuritis, or thiamine deficiency. Such disturbances have not been reported in articles dealing with the treatment of the menopause. This omission may not be inconsistent with our observation, since gonadotropin is excreted in the urine by women in the menopause, and the full therapeutic effect of estrogen is generally not considered to be achieved until enough has been given to cause the gonadotropin to disappear almost completely from the urine. The endocrine condition of our patients is not necessarily comparable to that of the menopausal patient. In addition, our patients had a vitamin B complex deficiency, and some had a pathologic condition of the liver.

The observations reported here and in our preceding articles strongly indicate a relation between the endocrine glands and the vitamin B complex, since the administration of an extract of the anterior lobe of the pituitary containing the growth-stimulating and gonadotropic factors cures or controls the lesions of a vitamin B complex deficiency when they are not entirely relieved by administration of the complex, and since the administration of estrogens induces or exaggerates the lesions of such a deficiency. Our observations present the problem but provide no definite explanation. We suspect that the anterior lobe of the pituitary secretes a hormone which directly or indirectly facilitates the utilization of the vitamin B complex and that estrogens either increase the demand for this hormone or suppress its secretion. The role the liver may play in the process is not so readily postulated.

## CONCLUSIONS

1. The administration of estrogens to persons with a subclinical vitamin B complex deficiency may cause the appearance of lesions characteristic of a (*a*) thiamine deficiency (polyneuritis), (*b*) nicotinic acid deficiency (pellagra) or (*c*) riboflavin deficiency (cheilosis).

2. It appears obvious that the estrogens do not aid in the utilization of the vitamin B complex. According to our observation, they appear either to increase the demand for or to suppress the utilization of the vitamin B complex. The role that the damaged liver may play is uncertain.

3. The appearance of tenderness and pain in the nasal mucosa appears to be a symptom of the full physiologic effect of estrogen similar to the changes in the vaginal mucosa, particularly in persons with a vitamin B complex deficiency.

4. These observations should not be interpreted in any way as a contraindication to the use of estrogens in the treatment of ovarian deficiency, as the patients whose cases are reported here gave evidence of vitamin B deficiency before therapy with an estrogen was begun.

# ORTHOSTATIC CIRCULATORY INSUFFICIENCY

ITS OCCURRENCE IN TABES DORSALIS AND ADDISON'S DISEASE

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The maintenance of an adequate circulation despite change in posture, as from the horizontal to the vertical position, is accomplished by mechanisms which insure an equitable distribution of blood. In normal persons, the assumption of an erect position is attended by an increase in peripheral vasoconstriction, particularly in the arterioles of the splanchnic area,<sup>1</sup> by acceleration of the heart<sup>2</sup> and by a greater tonus of the skeletal musculature.<sup>3</sup> Impairment of the capacity for postural adaptation, as a result of the failure of any of these factors, favors the development of orthostatic circulatory insufficiency, with stasis of blood in dependent areas and reduction of the cerebral blood supply. As a rule, this defect is temporary and occurs in patients weakened by illness.<sup>4</sup> However, it is not uncommon in persons with low blood pressure,<sup>5</sup> with a history of postural symptoms and a condition of noticeably subnormal

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From the second medical service (Dr. Eli Moschcowitz) of the Mount Sinai Hospital.

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2. MacWilliam, J. A.: Postural Effects on Heart Rate and Blood Pressure, *Quart. J. Exper. Physiol.* **23**:1 (Aug.) 1933.

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4. Weiss, S.: Syncope and Related Syndromes, in Christian, H. A.: *Oxford Medicine*, New York, Oxford University Press, vol. 2, pt. 1, p. 250.

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weight<sup>6</sup> or with the "effort syndrome."<sup>7</sup> It occurs not infrequently in normal subjects at high altitudes, after strenuous exercise<sup>8</sup> or merely on standing immobile,<sup>3b</sup> for example, in a soldier standing at attention. Anesthesia, shock and various unconscious states are associated with the depression of compensatory responses, and under these conditions any change from the horizontal position endangers life.<sup>9</sup> Fall in blood pressure, narrowing of the pulse pressure and increasing tachycardia, as well as vertigo and syncope, after assumption of an erect posture are sensitive indications of difficulty in offsetting the effect of gravity on the blood column.<sup>10</sup> The principal causes of this form of circulatory insufficiency include lowering of the tonus of the vasomotor system,<sup>11</sup> excessive capillary dilatation,<sup>8</sup> hypotonus of the skeletal muscles<sup>3</sup> and diminished venous tone.<sup>12</sup>

Insufficiency of circulation during maintenance of the erect position, usually temporary and mild, may be extreme and persistent, as it was in 3 patients whose cases were reported, in 1925, by Bradbury and Eggleston<sup>13</sup> as examples of a new syndrome, "postural hypotension." In each case, rising from a recumbent to a standing position was attended by a prompt, pronounced fall in systolic and in diastolic blood pressure, a slow unchanging pulse rate, dizziness and syncope. Additional findings were (a) increased distress during the heat of summer, (b) anhidrosis, (c) signs of slight and indefinite disease of the central nervous system, (d) high normal blood urea, (e) anemia and (f) a low basal metabolic rate. Results of pharmacologic studies indicated that the responsiveness of the vasoconstrictor endings to epinephrine was impaired or lost. The vascular reactions were those "which would be expected if the whole peripheral vascular bed were always wide open, inelastic and capable of accommodating the major portion of the blood

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6. Ghrist, D. G.: Variations in Pulse and Blood Pressure with Interrupted Change in Posture, *Ann. Int. Med.* **4**:945 (Feb.) 1931.

7. Lewis, T.: *The Soldier's Heart and the Effort Syndrome*, ed. 2, London, Shaw & Sons, Ltd., 1940.

8. Mateef, D., and Schwartz, W.: Die orthostatische Kreislaufkollaps, Gravi-tationsschock, bei verminderten Luftdruck, *Arch. f. d. ges. Physiol.* **236**:77, 1935.

9. Best, C. H., and Taylor, M. M.: *Physiological Basis of Medical Practice*, Philadelphia, William Wood & Company, 1937, p. 220. Hill,<sup>1a</sup> Hill and Barnard.<sup>1b</sup>

10. Schneider, E. C., and Truesdall, H.: A Statistical Study of Pulse Rate and the Arterial Blood Pressures in Recumbency, Standing and After a Standard Exercise, *Am. J. Physiol.* **61**:429 (Aug.) 1922. Crampton, C. W.: The Gravity Resisting Ability of the Circulation: Its Measurement and Significance, *Am. J. M. Sc.* **160**:721 (Nov.) 1920.

11. Hill.<sup>1a</sup> Hill and Barnard.<sup>1b</sup>

12. Weiss, S., and Haynes, F.: The Nature of Circulatory Collapse Induced by Sodium Nitrite, *J. Clin. Investigation* **16**:73 (Jan.) 1937.

13. Bradbury, S., and Eggleston, C.: Postural Hypotension: Report of Three Cases, *Am. Heart J.* **1**:73 (Oct.) 1925.

volume of the body." The syndrome was believed to be due to some extensive and peculiar disturbance in the functional capacity of the vegetative nervous system.

Analysis of 50 adequately studied cases of "postural," or "orthostatic," hypotension reported since 1925 indicated that this syndrome is not a uniform clinical entity.<sup>14</sup> (Twenty-four cases<sup>15</sup> were excluded

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from the total number because of insufficient clinical data or because the postural defect was slight and transient.) The only constant and characteristic feature of these cases was an immediate and persistent fall in blood pressure on standing. In two thirds of the cases there was a drop in systolic pressure of at least 50 mm. of mercury, with a smaller, corresponding change in diastolic pressure, while in the remainder the fall in blood pressure was less. Orthostatic vertigo and syncope were common, but some patients with marked fluctuations in blood pressure were relatively asymptomatic, in contrast to others who were intolerant of slight changes. The erect position had a variable effect on pulse rate. In half the subjects the heart failed to accelerate normally on standing; in an equal number cardiac acceleration was normal or excessive. Hypofunction of the sweat glands, varying in intensity and extent, was mentioned in slightly more than one third of the cases. Seventy-five per cent of the patients were male, and 50 per cent were 50 years of age or older.

Of particular interest was the problem of the cause of deficient postural compensation in these cases. In most instances the condition occurred in otherwise healthy persons, and the syndrome was regarded as an abnormality of the sympathetic nervous system in which a failure of reflex vasoconstriction accompanied change to an erect position. Both the nature and the site of the pathologic process causing this abnormality were obscure. However, in about one quarter of the reported cases postural hypotension was associated with disease of the nervous system,<sup>16</sup>

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16. Strisower,<sup>14d</sup> Allen and Magee,<sup>14k</sup> Croll, Duthie and MacWilliam,<sup>14n</sup> Ellis and Haynes,<sup>14t</sup> Ewert,<sup>14z</sup> Baker,<sup>14a'</sup> Thomas,<sup>14b'</sup>

myasthenia gravis<sup>148</sup> or adrenal insufficiency.<sup>148</sup> Association with such conditions suggested the relation of orthostatic circulatory disorders to nervous and endocrine dysfunction and indicated the need of investigating all cases of inadequate postural adaptation for etiologic factors.

It is the purpose of this communication to illustrate the foregoing material by the report of 3 cases of tabes dorsalis and 1 case of Addison's disease in which impressive defects in postural adaptation were observed. In addition, results of studies regarding carotid sinus hypersensitivity and the use of desoxycorticosterone acetate in treating patients with orthostatic circulatory difficulties will be presented.

#### REPORT OF CASES

CASE 1.—A 59 year old white salesman was admitted to the second medical service of Mount Sinai Hospital on Nov. 1, 1939 because of weakness and frequent fainting. He acquired syphilis at the age of 20 and received two courses of anti-syphilitic therapy, the first when he was 20 and the second when he was 40. In 1932 he noticed the onset of recurrent epigastric pain, weakness and vertigo. He had episodes of nausea and vomiting, often terminating in syncope. Since 1937 he found it difficult to rise from a recumbent to a standing position because of weakness, vertigo and occasional syncope on the assumption of the erect posture. Getting out of bed in the morning became a trying task, requiring repeated attempts to stand. Standing for a short time or tilting the head back to look up led to uncomfortable weakness and dizziness. Lowering the head between the legs or assuming a recumbent position promptly relieved these symptoms. He became completely incapacitated and was unable to engage in any form of sustained effort. On the day of admission to the hospital he fainted while being examined by a physician, who advised hospitalization.

*Physical Examination.*—The patient appeared emaciated and chronically ill. His teeth were dirty and carious. There was a small angioma on the right buccal mucous membrane, but no buccal pigmentation. The right optic disk was pale; the left, normal. The choroidal vessels could be easily seen and formed a yellow gyrate pattern, indicating well marked choroidal sclerosis. The pupils were round, in mid-dilatation and fixed to light and in accommodation. The lungs were clear. The heart sounds were poor, but the heart was otherwise normal. The abdomen was scaphoid, with lax walls. Generalized muscular hypotonia, especially in the lower extremities, was detected on neurologic examination; deep reflexes were diminished in the upper extremities and were not elicitable in the lower, even with reenforcement. The abdominal reflexes were present but exhaustible. There were no pathologic reflexes. Touch sensation (cotton wool) was relatively normal. Sensitivity to pinprick was diminished in both lower extremities to the inguinal regions and in both arms to above the elbows. There were narrow, poorly defined bands of hypalgesia on the trunk; vibratory sensation was absent in both lower extremities to above the iliac crests. Position sense was lost in the toes and in the fingers of the left hand. Deep tendon pain was diminished.

When the patient stood erect, he swayed noticeably, became weak, and had to be supported to prevent his falling. A pulse could not be palpated at the wrist while he was in the erect position. His blood pressure while he was standing was 60 systolic and 50 diastolic as compared with 120 systolic and 80 diastolic

measured a few minutes before while he had been recumbent. The clinical impression was *tabes dorsalis* associated with postural hypotension, which was apparently the basis for the recurrent dizziness and fainting.

*Laboratory Data.*—The concentration of hemoglobin was 86 per cent (100 per cent = 16 Gm. per hundred cubic centimeters), and the white blood cell count was 7,700, with 71 per cent polymorphonuclear leukocytes, 2 per cent eosinophils, 5 per cent monocytes and 22 per cent lymphocytes. The urine was clear with an acid reaction, a specific gravity of 1.020, a faint trace of albumin and, on microscopic examination, an occasional white blood cell. Gastric analysis showed normal acidity. Chemical analysis of the blood revealed urea nitrogen to be 16 mg. per hundred cubic centimeters; sugar, 95 mg. per hundred cubic centimeters; total protein, 7.2 Gm. per hundred cubic centimeters, and icteric index, 3. The result of the dextrose tolerance test was normal. After three days of a salt-poor diet containing less than 1 Gm. of sodium chloride daily, the content of sodium in the blood was 140 milliequivalents per liter. The Wassermann reaction of the blood was negative. Lumbar puncture yielded crystal clear spinal fluid under normal pressure. The fluid contained 55 lymphocytes per cubic millimeter. The reaction for globulin was positive. The Wassermann reaction of the spinal fluid was 4 plus, and the colloidal gold curve was paretic in type. The total protein content of the spinal fluid was 72 mg. per hundred cubic centimeters.

The basal metabolic rate was —30 per cent. The venous pressure was 4.5 cm. of blood, with no rise on pressure on the right upper quadrant of the abdomen for one minute. An electrocardiogram showed regular sinus rhythm, left axis deviation and semi-inversion of the P and T waves in lead III.

*Effect of Posture on Blood Pressure and Pulse Rate.*—Elevation of the patient on a mechanical tilt table 80 degrees above the horizontal was attended by an immediate fall in the systolic and the diastolic blood pressure from 120 to 60 and from 70 to an undetermined figure, respectively; the pulse rate increased from 72 to 86. Sudden lowering of the patient to the horizontal was accompanied by a return of blood pressure to normal. The fall in blood pressure on elevation could not be prevented by the application of an abdominal binder.

*Effect of Vasoconstrictor Substances.*—Intravenous injection of 2 minims (0.12 cc.) of a 1:1,000 solution of epinephrine hydrochloride caused a rise in blood pressure to 240 systolic and 140 diastolic ten seconds after injection and an acceleration of the pulse rate to 190. The fall in blood pressure during maintenance of the erect posture was prevented for nine minutes. Inhalation of a mixture of 25 per cent carbon dioxide and 75 per cent oxygen caused a rise in blood pressure from 120 to 240 systolic and from 80 to 120 diastolic after thirty seconds of administration of the gas with the patient in a horizontal position. Elevation of the patient was attended by a fall in blood pressure to hypotensive levels within two minutes. The mixture of gases produced no pressor response if the patient maintained an erect position after the blood pressure had fallen; however, resumption of a horizontal position after this stimulus had been removed was followed by a transient pressor response. Intravenous administration of 10 mg. of paredrinol (*α*-N-dimethyl-p-hydroxyphenethylamine) caused a rise in blood pressure to 240 systolic and 120 diastolic and prevented the fall in blood pressure for ten minutes. These findings indicated the sensitivity of the vasoconstrictor endings to pressor influences.

*Stimulation of the Carotid Sinus.*—Mechanical stimulation of the right carotid sinus with the patient recumbent was associated with bradycardia, a fall in the

systolic and the diastolic blood pressure, syncope and generalized convulsions. Periods of asystole, lasting seven to eight seconds, were recorded electrocardiographically during sinus stimulation. These phenomena could be elicited more easily and more frequently with the patient in the sitting position. The left carotid sinus was less sensitive to stimulation than the right. Apparently, none of the symptoms were related to sudden turning of the head or wearing of a tight collar, factors often precipitating syncope in cases of the carotid sinus syndrome.

*Circulation Time.*—The circulation time was measured as the patient was placed in various positions with the aid of a mechanical tilt table. Three cubic centimeters of a 20 per cent solution of decholin sodium and 2.5 Gm. of saccharin in 3 cc. of distilled water were used as test substances and were injected into a right antecubital vein. The decholin end point, a bitter taste, was sharper than the saccharin point, a sweet taste. At the time of the first determination the patient's blood pressure fell from 88 systolic and 64 diastolic in the horizontal position to 40 systolic and an undetermined diastolic level in the vertical position. When he was in the former position the circulation time of decholin was twenty-two seconds and that of saccharin twenty-six seconds. When the patient was in the vertical position no satisfactory response could be obtained with either substance. When he was lowered after each failure, no definite end point was obtained. During these studies he complained of vertigo and blurring of vision in the erect posture, and it was felt that the failure to obtain a response while he was in the erect position was due in part to his inability to cooperate subjectively, a result of cerebral anemia.

Ten days later, after three days of therapy with desoxycorticosterone acetate, these studies were repeated. At this time postural hypotension was not present and the blood pressure was maintained at 110 systolic and 60 diastolic whether the patient was recumbent or erect. When he was recumbent the circulation time of decholin was nineteen seconds and the circulation time of saccharin was thirty seconds; after he assumed an erect position the respective times were sixteen and twenty-nine seconds. He was free of postural symptoms.

*Treatment.*—The use of a variety of drugs and mechanical measures to control the postural hypotension was without impressive benefit. Ephedrine sulfate, neo-synephrin hydrochloride and paredrine hydrobromide (para-hydroxy- $\alpha$ -methylphenethylamine hydrochloride) in adequate doses by mouth caused little, if any, subjective and no objective improvement. A tight abdominal binder did not reenforce the postural mechanisms. Elastic bandages, from the ankles to the mid-thighs, were uncomfortable and did not prevent the orthostatic fall in blood pressure. On the other hand, the tabes dorsalis was controlled satisfactorily by intramuscular injection of a suspension of bismuth subsalicylate in oil for a period of eight months.

The failure to remedy the postural defect by the usual measures led to an empiric study of the effect of sodium chloride and desoxycorticosterone acetate. Preliminary administration of 9 Gm. of sodium chloride daily for ten days resulted in no definite change. However, the addition of intramuscular injections of desoxycorticosterone acetate in oil (5 mg. daily) was followed promptly by an increase in weight of from 139 to 144 pounds (63 to 65.3 Kg.) in six days and amelioration of the postural hypotension. The blood pressure could be maintained without change for five to ten minutes, while the patient remained erect, and the subsequent fall was less marked. On several occasions blood pressure readings of 150 systolic and 100 diastolic were obtained with the patient recumbent. The circulation times with the patient in the horizontal and in the vertical position

were approximately the same, in contrast to his inability before the use of desoxycorticosterone to remain erect long enough for us to obtain an end point. The patient stated that he felt more vigorous and was capable of greater physical activity. The sodium content of the blood after injections of desoxycorticosterone acetate was 145 milliequivalents per liter and the chloride content 105 milliequivalents per liter. The blood volume was 93 cc. per kilogram (congo red test). The carotid sinus hypersensitivity was unchanged.

Cessation of therapy with desoxycorticosterone acetate caused prompt reappearance of marked postural hypotension and associated symptoms. Subsequent injections of the drug were accompanied again by the same improvement, as a result suggesting a specific response. Satisfactory improvement was obtained with as little as 1.2 mg. of desoxycorticosterone acetate daily, given with 9 Gm. of sodium chloride. The use of the drug was attended by a slight transient edema of the legs and face but not by other untoward symptoms or by electrocardiographic changes.

Four pellets of crystalline desoxycorticosterone acetate, each weighing approximately 125 mg., were implanted subcutaneously below the angle of the right scapula. After implantation the patient could stand comfortably for thirty to sixty minutes. During such periods the blood pressure fell slowly from 120 to 70 systolic and from 80 to 60 diastolic. The fall was neither as marked nor as prompt as before desoxycorticosterone acetate therapy. The pellets stayed in situ for nineteen weeks, with only slight and unimpressive control of the postural hypotension after the patient left the hospital. It was felt that the daily dose supplied by these pellets (about 1.2 mg.) was inadequate for the demands of life outside the hospital. During this period extradietary sodium chloride was withheld. Supplementary injections of desoxycorticosterone acetate in oil (5 mg. two to three times weekly) seemed of some benefit, but this was less striking as compared with observations during hospitalization. When the pellets were removed, nineteen weeks after implantation, their original weight was reduced by about half. A salt deprivation test, performed two weeks later, revealed no evidence of adrenal insufficiency. After three days of deprivation the sodium content of the blood was 138 milliequivalents per liter and the chloride content 103 milliequivalents per liter. The basal metabolic rate was —14 per cent. The sugar tolerance curve was normal. However, the patient complained of increased weakness, was bedridden and had a return of pronounced orthostatic hypotension. Restitution of daily injections of 5 mg. of desoxycorticosterone acetate in oil led to a gain in weight, a rise in blood pressure and a more sustained blood pressure during maintenance of an erect position.

CASE 2.—A 54 year old white man, a German refugee, was admitted to the second medical service on July 11, 1940 because of weakness, vertigo and vomiting for one month. On a previous admission to the hospital, in May 1940, a diagnosis of *tabes dorsalis* and cord bladder was made. At that time moderate loss in weight, thin lax abdomen, palpable liver, absence of ankle and knee jerks, positive Biernacki and Abadie signs and loss of vibratory sensation over the sacral area were observed. The pupils were irregular but reacted well to light and in accommodation. Repeated Wassermann tests of the blood gave negative results, even after provocative injections of a suspension of bismuth subsalicylate in oil and neoarsphenamine. The Wassermann reaction of the spinal fluid was positive. The colloidal gold curve was tabetic in type.

Shortly after discharge the patient began to vomit frequently, especially in the morning after getting out of bed. He felt weak and dizzy at such times and noticed that his symptoms, especially vertigo, were relieved by lying down.

The patient was seen by one of us (W. M. H.) in the outpatient clinic, and his history associated with the tabes prompted a study of the effect of posture on pulse and blood pressure. A definite postural fall in blood pressure was noted, and the patient was readmitted to the hospital for study. Results of the physical examination were unchanged from the time of his first admission. There was no evidence of abnormal sweating; the urine contained albumin and many white blood cells; the electrocardiogram was normal; the basal metabolic rate was  $-15$  per cent; the blood count was normal; the blood per hundred cubic centimeters contained 17 mg. of nitrogen and 610 mg. of chlorides; its carbon dioxide-combining power was 59.5 volumes per cent, and the Wassermann reaction of the blood was negative.

*Postural Studies*.—Rising from a horizontal to a vertical position led to an immediate fall in blood pressure from 110 to 75 systolic and from 70 to 50 diastolic. Standing for five minutes led to a further drop, to 60 systolic and 50 diastolic. The pulse rate increased from 78 when the patient was in the horizontal position to 88 when he was in the vertical position. Similar results were obtained during passive elevation of the patient on a mechanical tilt table. The degree of the orthostatic fall varied from day to day but was always present and was most marked in the morning. The circulation time of decholin was fifteen seconds both when the patient was recumbent and when he was standing. Pressure on the right carotid sinus with the patient upright led to an imperceptible pulse, mild collapse and transient blurring of vision. Sinus stimulation with the patient recumbent produced neither symptoms nor changes in pulse and blood pressure.

*Treatment*.—Daily injections of 5 mg. of desoxycorticosterone acetate in oil were given for sixteen days. This therapy was associated with a rise in blood pressure. Readings of 150 systolic and 90 diastolic were obtained often while the patient was recumbent, as compared with the reading of 110 systolic and 70 diastolic made on admission. Although an orthostatic fall in blood pressure persisted, a higher pressure could be maintained for a considerably longer period while he was erect. When he maintained a vertical position for thirty minutes, his blood pressure dropped from 120 to 90 systolic and 78 to 64 diastolic. The patient gained weight and said he felt much improved.

CASE 3.—A white woman aged 44 was admitted to the service of Dr. I. S. Wechsler on Aug. 11, 1940. Her chief complaint was pain in the back and legs for four years. In 1936 a routine Wassermann reaction of the blood was positive. She had received antisyphilitic therapy for eighteen months and then discontinued treatment, despite the fact that her serologic reactions were still positive. Throughout treatment and up to the time of admission she experienced episodes of numbness and tightness across the chest and recurrent shooting pains arising in the lumbar region and radiating down both legs. About one year before entry she noticed the onset of vertigo, weakness and frequent headaches. These symptoms were relieved by lying down and were precipitated by rising from the recumbent position, particularly on attempting to get out of bed in the morning.

*Physical Examination*.—The patient was well developed and somewhat euphoric, with small irregular pupils which reacted adequately to light and in accommodation. The heart was enlarged. The aortic second sound was loud and bell-like. The lungs were clear. Deep reflexes were hyperactive in both upper extremities. The left knee jerk and the ankle jerks could not be obtained. Superficial reflexes were intact. There was a positive Abadie sign on the left. Deep sensation was diminished and delayed on the right. Vibratory position and superficial sense modalities were normal. The clinical impression was tabes dorsalis.

*Laboratory Data.*—The urine and the blood count were normal. The spinal fluid was clear and under normal pressure; it contained 7 monocytes per cubic millimeter and had a total protein content of 60 mg. per hundred cubic centimeters. The colloidal gold curve was tabetic in type. The Wassermann reactions of the blood and the spinal fluid were positive. The blood per hundred cubic centimeters contained 15 mg. of urea nitrogen and 80 mg. of sugar.

*Postural Reactions and Carotid Sinus Reflexes.*—The history of postural symptoms prompted the study of the effect of changes in posture on pulse rate and blood pressure. A definite orthostatic fall in blood pressure associated with increasing tachycardia was observed. The blood pressure dropped from 152 to 108 systolic and remained at 88 diastolic within seven minutes after a change from a recumbent to an erect posture. This was associated with an increase in pulse rate from 90 to 124 beats per minute and the onset of weakness, vertigo and profuse diaphoresis.

Pressure on the right carotid sinus with the patient recumbent produced immediate asystole followed within a few seconds by syncope and clonic convulsions. Similar results followed pressure on the left carotid sinus. Atropinization abolished the abnormal sensitivity of the carotid sinus to mechanical stimulation. There was no history of spontaneous symptoms attributable to this sensitivity.

*Course and Treatment.*—The patient was treated with tryparsamide, without any disturbance in visual fields or acuity. Because of her orthostatic defect, she was given 25 mg. of ephedrine sulfate three times daily. The use of the drug, during a three week period of observation, was associated with dramatic relief of vertigo and weakness while standing. There was no change in the vascular reactions or in the degree of carotid sinus sensitivity to mechanical stimulation.

CASE 4.—A white man, a 46 year old delicatessen clerk, consulted one of us (W. M. H.) in August 1940. For a month he had been troubled with constant weakness and frequent episodes of vertigo. His past history included recurrent attacks of epigastric pain since 1937 and treatments for a suspected pyloric ulcer in 1939. In May 1940 while on a restricted diet for a gastric disorder, he lost weight and strength and was observed for one week in a hospital. On discharge he was unimproved. Examination had revealed no cause for his complaints. During the subsequent weeks asthenia and loss of weight continued. In addition, he found it difficult to stand because of vertigo. This symptom was associated with the erect posture and was relieved by lying down. On one occasion he fainted after a vomiting spell.

*Physical Examination.*—The patient appeared chronically ill, with a pressure which fell from 110 to 70 systolic and 70 to 60 diastolic after he stood for two minutes. His pulse rate increased from 80 beats per minute while he was recumbent to 108 when he stood erect. Pressure on the right carotid sinus was poorly tolerated only when he was in an erect position. There were patches of black pigmentation on the gums and buccal mucosa. The genitals were highly pigmented. The patient thought his skin was somewhat darker than previously, although the presence of a recent sun tan made it difficult to be certain. The symptoms and findings suggested Addison's disease, and on Aug. 14, 1940 he was referred to the second medical service at Mount Sinai Hospital.

On admission, the additional history of a recent craving for salty food was obtained. Physical examination confirmed the aforementioned observations. His blood pressure was 86 systolic and 60 diastolic when he was recumbent and 70 systolic and 60 diastolic after he had stood one minute. The concentration of hemoglobin was 100 per cent, and the white blood count was 7,600, with a normal dif-

ferential count. The urine was normal. The Wassermann reaction of the blood was negative. An electrocardiogram showed no abnormality. The blood per hundred cubic centimeters contained 24 mg. of urea nitrogen, 85 mg. of sugar and 525 mg. of chlorides (as sodium chloride). The sodium content of the blood was 133 milliequivalents per liter. A roentgenogram of the abdomen was negative for calcification of the adrenals. The dextrose tolerance curve was flattened. The Mantoux test was positive in a dilution of 1:100,000.

*Course and Treatment.*—The history, physical findings and laboratory data justified a diagnosis of Addison's disease, and therapy with sodium chloride and desoxycorticosterone acetate was started. The use of 12 Gm. of sodium chloride daily was associated with relief of weakness and a rise in weight from 133 to 140 pounds (60.3 to 63.5 Kg.) in a week. The hematocrit reading fell from 41 to 36 per cent and the blood urea nitrogen from 24 to 15 mg. per hundred cubic centimeters. The postural fall in blood pressure remained. His blood pressure while he lay recumbent was 115 systolic and 90 diastolic but dropped to 96 systolic and 66 diastolic when he stood erect. After three weeks improvement seemed stationary. Administration of extra sodium chloride was stopped, and the patient was given daily intramuscular injections of 5 mg. of desoxycorticosterone acetate in oil. After seven injections his weight increased to 148 pounds (67.1 Kg.) and his blood pressure rose to 145 systolic and 90 diastolic. Postural hypotension was no longer present. At this time the hematocrit reading was 32 per cent. The patient was scarcely recognizable; his complexion was lighter, and he stated that he felt better than he had in years.

Desoxycorticosterone acetate and extra sodium chloride were discontinued. In nine days the patient lost 10 pounds (4.5 Kg.), and the hematocrit reading rose from 32 to 40 per cent. The blood pressure dropped from 140 to 120 systolic and from 90 to 80 diastolic. However, orthostatic hypotension was not observed. To obtain metabolic evidence of adrenal insufficiency, we placed him on a salt-poor diet (containing less than 1 Gm. of sodium chloride daily) for three days. On the second day he complained of extreme weakness and fatigue, and a fall in blood pressure while he maintained an erect position was present for the first time since the use of desoxycorticosterone acetate. His blood pressure dropped from 140 systolic and 90 diastolic while he was recumbent to 110 systolic and 80 diastolic after he stood for two minutes. On the third day he complained of nausea and extreme weakness and vomited several times. He was prostrate; his blood pressure was 85 systolic and 60 diastolic, and his pulse rate was 125 beats per minute. Two hours before this episode the horizontal blood pressure was 120 systolic and 80 diastolic. He presented the picture of acute adrenal insufficiency. Intravenous administration of physiologic solution of sodium chloride and injections of desoxycorticosterone acetate were followed by prompt improvement. The content of sodium in the blood at the time of the crisis was 127 milliequivalents per liter, a level indicating adrenal cortical insufficiency.

#### COMMENT

The preceding cases represent varying degrees of orthostatic insufficiency of the circulation, a state characterized by falling blood pressure, diminished venous return and impaired cerebral blood supply during maintenance of an erect posture. Attacks of syncope were seen only in 1 of the patients (case 1), in whom the orthostatic fall in blood pres-



sure was immediate and most marked. The absence of syncope in many cases of postural hypotension was attributed by Barker<sup>14j</sup> to a compensatory increase in heart rate sufficient to maintain an adequate cardiac output. In cases in which syncope was lacking he noted that a greater increase in pulse rate was associated with falling blood pressure than in cases in which syncopal attacks were frequent and in which cardiac acceleration was usually slight or absent. In each of our cases, an increase in heart rate occurred when the patient stood erect, and in 1 (case 3) standing was accompanied by increasing tachycardia. In all cases weakness and vertigo during maintenance of an erect posture were annoying symptoms. It is interesting that the cause of these two symptoms remained obscure for a considerable period in the 3 cases of *tabes dorsalis* in which orthostatic difficulty was finally recognized. In our fourth case these symptoms were promptly ascribed to an inadequate postural response. This and other findings were consistent with a diagnosis of Addison's disease.

The presence of defective postural adaptation and the consequent orthostatic circulatory insufficiency in our 3 cases of *tabes dorsalis* illustrates the relation of nervous disease to this abnormality. Although Bradbury and Eggleston<sup>13</sup> noted irregular pupils and abnormal reflexes in their original report of cases of postural hypotension, Strisower<sup>14d</sup> was the first to report comparable orthostatic difficulty in patients with an extensive nervous disease, such as *tabes dorsalis*. He noted defective responses to changes in posture in 13 of 20 tabetic patients whom he studied and ascribed them to involvement of spinal vasomotor centers and tracts. Subsequently, Ellis and Haynes<sup>14t</sup> recorded 2 cases of *tabes dorsalis* with postural hypotension and noted mild postural depression of blood pressure in 8 of 15 cases of *tabes*. In 2 other cases of postural hypotension described in their report syringomyelia and transverse myelitis, respectively, were present. On the other hand, the study by the same authors of a group of cases of combined system disease, advanced multiple sclerosis, marked syringomyelia, amyotrophic lateral sclerosis and transverse myelitis failed to reveal an inadequate response of the blood pressure during maintenance of erect posture. These cases indicated that extensive disease of the brain and spinal cord can exist without a disturbance of the postural blood pressure reflex. Ellis and Haynes expressed the belief that the orthostatic fall in blood pressure in patients with neurologic disease resulted from damage to the vasomotor reflex arc and stated that the etiologic factor was apt to be multiple, since the reflex arc could be interrupted at different levels. They suggested that the lesion was hypothalamic rather than spinal.

Signs of a disseminated disease of the central nervous system of unknown cause were present in cases of postural hypotension reported by Ganshorn and Horton,<sup>14i</sup> Baker<sup>14n'</sup> and Ewert.<sup>14z</sup> Baker suggested

that patchy sclerosis of the brain and the spinal cord might be the result of the intermittently disturbed circulation of these organs incident to postural changes, rather than the cause of this form of circulatory weakness. Hemianopia and aphasia in the case of postural hypotension reported by Allen and Magee<sup>14k</sup> were attributed to sclerosis of the cerebral vessels. Adie's syndrome (pseudo Argyll Robertson pupil and absence of knee jerks) was noted in the case reported by Croll, Duthie and MacWilliams.<sup>14n</sup> Thomas<sup>14b'</sup> described a remarkable case of an arteriosclerotic man with postural hypotension who suffered from transient episodes of right hemiplegia in the erect posture. It is interesting that postural hypotension and regional anhidrosis have been produced by anterior rhizotomy, splanchnic resection and excision of abdominal sympathetic ganglions for severe essential hypertension.<sup>17</sup>

Several points are called to mind by the foregoing consideration of the occurrence of impaired orthostatic circulatory adjustment in patients with nervous disease. Obviously, the recognition of such deficiency may clarify the significance of dizziness and fainting in some patients with neurologic disorders. Recognition of this abnormality, even to a mild degree, is of particular importance in any such patient before a surgical procedure or any form of therapy that may favor the onset of circulatory collapse—for example; hyperthermia or malaria therapy. Finally, it has been stated that "when the anatomic pathways of this [vasomotor] reflex have been traced with greater exactitude, the measurement of blood pressure in different bodily positions may furnish evidence as to the presence or location of a lesion of the central nervous system."<sup>14t</sup>

An exceptional feature of 2 of our cases (1 and 3) was the presence of hypersensitivity of the carotid sinus. In each instance, mechanical stimulation of the sinus with the patient recumbent produced cardiac asystole, a fall in blood pressure, syncope and convulsions. An analysis of 53 cases of postural hypotension and of 24 cases of a milder degree of inadequate postural adaptation revealed hypersensitivity of the carotid sinus in only 4 cases. In most reports the reactivity of the carotid sinus reflexes was not mentioned. Ellis and Haynes,<sup>14t</sup> who studied these reflexes in 6 cases, found a mildly hyperactive reaction in only 1, a case of tabes. Hughes and Yusaf<sup>14p</sup> elicited a prompt fall in pulse rate on carotid pressure in 1 case. In a case reported by Ewert<sup>14z</sup> stimulation of the carotid sinus was followed by asystole for several seconds and an atrioventricular block. Atropinization prevented this response. Thomas<sup>14b'</sup> reported a case in which pressure on the carotid sinus dur-

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17. Brown, G. E.; Craig, W. McK., and Adson, A. W.: The Treatment of Severe Essential Hypertension: Effects of Surgical Procedures Applied to the Sympathetic Nervous System, *Minnesota Med.* **18**:134 (March) 1935.

ing maintenance of the erect posture resulted in rapid deep breathing, bradycardia and syncope. An electrocardiogram showed a dropped beat, with a ventricular pause lasting two and one-half seconds. On the other hand, in cases recorded by Browne and Horton,<sup>14c</sup> Davis and Shumway<sup>14v</sup> and Korns and Randall,<sup>14u</sup> no abnormalities were detected after stimulation of the carotid sinuses.

The occurrence of carotid sinus hypersensitivity in patients with orthostatic circulatory difficulties is of considerable interest, since it has been suggested that the latter abnormality may result from a disturbance of the regulating function of the carotid sinus. Normally, a fall in blood pressure within the sinus produces reflex vasoconstriction and cardiac acceleration.<sup>18</sup> Hering<sup>19</sup> reported prevention of these reflex responses in dogs by denervation of the sinuses, which process indicated a possible relation between the insensibility of the carotid pressoreceptive mechanism and the depression of blood pressure after assumption of the erect posture. Thus far, results of clinical studies have failed to support the concept of abnormal sensitivity of the carotid sinus in cases of orthostatic depression of blood pressure. Ferris, Capps and Weiss<sup>20</sup> found no relation between postural hypotension and hypersensitivity of the sinuses in a large carefully studied group of patients with carotid sinus syncope. In most patients with this disorder, the hypersensitive reflexes could be elicited more easily in the sitting or standing position, a fact indicating the reenforcing effect of gravity on the excessive response to stimulation. As a rule, these patients did not react adversely to posture alone. Mild postural hypotension was present in only 1 of 32 cases. Denervation of the sinus by section of the carotid sinus nerve prevented further syncopal attacks but did not lead to impairment of orthostatic adjustment. Similarly, Ask-Upmark<sup>21</sup> concluded that the clinical evidence does not support the contention that abnormalities of the carotid sinus reflexes are of etiologic significance in human postural hypotension.

In 2 of our cases and in the 4 cases recorded in the literature, sinus stimulation was associated with reflex bradycardia, a condition which would seem to indicate an increased vagal influence on the heart rate.

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18. Heymans, C.; Bouckaert, J. J., and Regniers, P.: *Le sinus carotidien et la zone homologue cardio-aortique*, Paris, Gaston Doin & Cie, 1933, p. 285.

19. Hering, H. E.: *Ueber die Blutdruckregulierung bei Aenderung der Körperstellung mittels der Blutdruckzügler und das Zustandekommen der Ohnmacht beim plötzlichen Uebergang vom Liegen zum Stehen*, München. med. Wchnschr. **74**:1611 (Sept. 23) 1927.

20. Ferris, E. B., Jr.; Capps, R., and Weiss, S.: Carotid Sinus Syncope and Its Bearing on the Unconscious State and Convulsions, *Medicine* **14**:377 (Dec.) 1935.

21. Ask-Upmark, E.: The Carotid Sinus and the Cerebral Circulation, *Acta psychiat. et neurol.*, 1935, supp. 6, p. 1.

Although the significance of the association of reflex abnormalities of cardiovascular regulation with sinus stimulation must remain a matter for speculation, it may be pointed out that carotid sinus hypersensitivity, like defective postural adaptation, may accompany nervous disease. Weiss<sup>4</sup> stated that "syphilis of the central nervous system seems to bear a causative relation to carotid sinus syncope." In 4 of 32 cases studied by Ferris, Capps and Weiss<sup>20</sup> tabes dorsalis was present. It is perhaps more than coincidental that in cases of orthostatic circulatory insufficiency with hypersensitive carotid sinus reflexes reported by Ellis and Haynes, by Ewert and by ourselves there was definite evidence of nervous disease. Consequently, lesions affecting central vasomotor reflex pathways may be the common basis for the coexistence of the two disturbances in these cases.

Two of our patients (cases 2 and 4) in whom stimulation of the carotid sinus was well tolerated when in the recumbent position reacted adversely to this procedure when standing. There was a fall in blood pressure, blurring of vision and incipient collapse after such stimulation. These responses were likely due to an increased susceptibility to slight changes in pulse and blood pressure so induced in patients with already impaired postural adaptation.

Our fourth case has been presented to indicate that orthostatic circulatory insufficiency may be a feature of Addison's disease. In this case, the clinical picture was obscure until failure to maintain a normal blood pressure in the erect posture was detected. This symptom, as well as others, led to additional studies which confirmed the presence of adrenal insufficiency. It is remarkable, and perhaps not generally known, that Addison mentioned orthostatic weakness and syncope in his first report.<sup>22</sup> Duggan and Barr,<sup>14g</sup> however, were apparently the first to record extreme postural hypotension as the cause of syncope in a case of Addison's disease. This case is unique, for we were unable to find a record of a comparable degree of postural circulatory inadequacy in a patient with this disease. However, lesser degrees of defective postural adaptation in patients with adrenal insufficiency have been observed by Ghrist,<sup>6</sup> Porges,<sup>23</sup> Hanssen,<sup>24</sup> Ratner<sup>15d</sup> and Thaddea.<sup>25</sup> Ghrist stated that decrease or abnormality of the circulating adrenal hormone is probably a major factor in these abnormal reactions to pos-

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22. Addison, cited by Duggan and Barr.<sup>14g</sup>

23. Porges, O.: Ueber die Behandlung des Morbus Addison mit Cortigen und die Zusammenhänge der Krankheit mit dem Kohlenhydratstoffwechsel, *Wien. klin. Wchnschr.* **46**:185 (Feb. 10) 1933.

24. Hanssen, P.: Six Cases of Addison's Disease: Contributions to Diagnosis and Treatment, *Acta med. Scandinav.* **89**:426, 1936.

25. Thaddea, S.: Nebennierenrinde und Blutdruckregulation, *Endokrinologie* **21**:388, 1939.

tural change. Thaddea attributed this finding to a hypodynamic state of the vasoconstrictor mechanisms as a result of cortical insufficiency. In several cases the postural fall in blood pressure was eliminated by treatment with adrenal cortical extract.<sup>26</sup> In our patient the inability to offset the effects of gravity on the circulation during maintenance of a standing position was not abolished until desoxycorticosterone acetate was given, despite the administration of ample sodium chloride preceding the use of this drug.

In this connection may be mentioned Schellong's<sup>15a</sup> report of orthostatic hypotension in patients with Simmonds' disease (anterior pituitary insufficiency). He expressed the belief that postural difficulties were an early and characteristic symptom of the disorder and noted improvement in vascular reactions with extracts of the anterior lobe. Ratner<sup>15d</sup> described cases of a similar condition and suggested that loss of the adrenotropic factor was primarily responsible for postural inadequacy in Simmonds' disease. Rudsit<sup>15c</sup> treated 5 patients who had mild orthostatic hypotension with extract of the anterior lobe and noted the disappearance of the abnormal vascular reactions. The mild nature of the postural disorder in this group of cases, as well as the difficulties inherent in the proof of the diagnosis of anterior lobe insufficiency, casts some doubt on the actual significance of some of these reports, although in 1 of Schellong's cases autopsy revealed destruction of the anterior lobe by a brain tumor.<sup>15a</sup>

The impaired ability of patients with Addison's disease and perhaps of those with Simmonds' disease to compensate for postural change may be the result of specific hormonal deficiency or of general physical debility. Ellis and Haynes<sup>14t</sup> expressed the opinion that the postural hypotension of such patients was part of a general hypofunction of the sympathetic nervous system and of the muscular hypotonicity seen in these states. In favor of a nonspecific response is the fact that postural difficulties may be seen in weakened persons, especially in those who have lost weight.<sup>6</sup> Recent emphasis on the importance of normal nutrition to glandular function suggests that defective postural adaptation in asthenic patients may represent temporary depression of some endocrine function. In this regard, it is interesting that Mulinos and Pomerantz<sup>27</sup> produced changes in the endocrine glands of rats by inanition which were similar to changes seen after hypophysectomy.

The use of desoxycorticosterone acetate in 3 cases deserves brief comment. In our patient with Addison's disease the drug produced a prompt elevation in blood pressure and led to the disappearance of the

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26. Hanssen.<sup>24</sup> Thaddea.<sup>25</sup>

27. Mulinos, M. G., and Pomerantz, L.: Pseudo-Hypophysectomy: A Condition Resembling Hypophysectomy Produced by Malnutrition, *J. Nutrition* **19**:495 (May) 1940.

postural hypotension, which had been only partially removed by therapy with sodium chloride. Cessation of this therapy was followed by the reappearance of orthostatic circulatory weakness, which preceded the onset of an addisonian crisis. This response may be a sensitive sign of inadequate therapy in cases of adrenal insufficiency.

In 2 cases of defective postural adaptation without associated Addison's disease, several reasons prompted the trial of desoxycorticosterone. The occurrence of orthostatic difficulties in patients with Addison's disease has been mentioned. Moreover, we have observed, and recent studies have shown, that desoxycorticosterone acetate has a pronounced effect on blood pressure in patients with Addison's disease, producing prompt elevation of blood pressure to normal and in some instances appreciable hypertension.<sup>28</sup> It is interesting that Bradbury and Eggleston<sup>13</sup> considered hypoadrenia a possible cause of postural hypotension and that unsuccessful attempts to treat this defect as a manifestation of adrenal cortical hypofunction have been reported by Langston,<sup>14r</sup> who used adrenal cortical extract (eschatin) and by Capaccio and Donald<sup>14w</sup> and Davis and Shumway,<sup>14v</sup> who gave large doses of sodium chloride.

In the aforementioned 2 cases treatment with desoxycorticosterone acetate was associated with symptomatic improvement and with an increased capacity for physical effort. Orthostatic hypotension, though still present, developed less rapidly and frequently to a lesser extent. Both patients were able to maintain higher levels of pressure for prolonged periods in the upright position. In addition, a moderate but inconstant rise in the blood pressure occurred in the horizontal position. However, the favorable influence of the drug on vascular adaptation after assumption of an erect posture did not seem to depend on a general increase in arterial tension. Amelioration of orthostatic circulatory insufficiency was observed on several occasions in the absence of any significant elevation of the horizontal blood pressure. This change suggested that the drug led to a greater ability to maintain an adequate circulation in the upright position by some mechanism as yet undetermined. The need for utmost care in the clinical use of desoxycorticosterone has been emphasized by the serious complications that may

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28. Ferrebee, J. W.; Ragan, C.; Atchley, D. W., and Loeb, R. F.: Desoxycorticosterone Esters: Certain Effects in the Treatment of Addison's Disease, *J. A. M. A.* **113**:1725 (Nov. 4) 1939. McCullagh, E. P., and Ryan, E. J.: The Use of Desoxycorticosterone Acetate in Addison's Disease, *ibid.* **114**:2530 (June 29) 1940. Thorn, G. W., and Firor, W. M.: Desoxycorticosterone Acetate Therapy in Addison's Disease: Clinical Considerations, *ibid.* **114**:2517 (June 29) 1940. Soffer, L. J.; Engel, F. L., and Oppenheimer, B. S.: Treatment of Addison's Disease with Desoxycorticosterone Acetate, *ibid.* **115**:1860 (Nov. 30) 1940.

occur during the treatment of Addison's disease with this substance<sup>29</sup> and by the results of its administration in large doses to normal animals.<sup>30</sup>

#### SUMMARY

Orthostatic circulatory insufficiency, marked by falling blood pressure and by vertigo on assumption of an erect position, was observed in 3 patients with *tabes dorsalis* and in 1 with Addison's disease. The relation of this abnormality to nervous and to endocrine disease is reviewed briefly. Carotid sinus hypersensitivity was an unusual feature of 2 of the reported cases. The results of the treatment of 3 patients exhibiting postural circulatory difficulties, 1 with Addison's disease and 2 without clinical adrenal insufficiency, by means of desoxycorticosterone acetate are presented.

NOTE.—Since the completion of this paper, a study of orthostatic hypotension by MacLean and Allen<sup>31</sup> has been published. They concluded that in the syndromes of primary orthostatic hypotension and orthostatic tachycardia, as well as in secondary orthostatic hypotension following extensive sympathectomy for essential hypertension, there is an inherent defect in the ability to return venous blood to the heart while the patient stands. They were able to improve significantly the ability of the circulation to adapt itself to the erect posture in some patients by the use of the tilted "head-up" bed. They suggest that this improvement in postural vascular adaptability coincides with an increase in circulating blood volume and a definite increase in the content of extracellular fluid in the lower extremities.

Dr. Arthur Fishberg made valuable suggestions; Dr. I. S. Wechsler gave us permission to include case 3 in this series, and Dr. George W. Thorn, of Johns Hopkins Hospital, furnished the pellets of desoxycorticosterone acetate used in case 1. The Ciba Pharmaceutical Products, Inc., supplied part of the desoxycorticosterone (percorten) used in this study.

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# GOITER WITH ASSOCIATED MYASTHENIA GRAVIS

REPORT OF THREE CASES OF EXOPHTHALMIC GOITER AND  
ONE CASE OF ADENOMATOUS GOITER WITH  
HYPERTHYROIDISM

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Exophthalmic goiter with associated myasthenia is common, but exophthalmic goiter accompanied by myasthenia gravis of the bulbar type is rare. The first case of the association of these two diseases was reported by Rennie in 1908.<sup>1</sup> Ten additional cases of exophthalmic goiter and 1 case of adenomatous goiter with hyperthyroidism, all with myasthenia gravis, have been found recorded in the literature.<sup>2</sup> To this group we wish to add 3 more cases of exophthalmic goiter and 1 case of adenomatous goiter with hyperthyroidism combined with myasthenia gravis. In 1 of our cases subtotal thyroidectomy was performed successfully, with alleviation of symptoms of both diseases.

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From the Division of Medicine (Drs. Kowallis and Haines) and the Division of Surgery (Dr. Pemberton), the Mayo Clinic.

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## REPORT OF CASES

CASE 1.—A married woman aged 39 registered at the Mayo Clinic in November 1939. She complained of difficult speech of eleven days' duration and double vision of four days' duration. In 1933 her systolic blood pressure had been found to be as high as 168 mm. of mercury. In 1935 she had been noted to have prominent eyes. She was intolerant of heat. The presence of a goiter had been suspected, but it had not been verified. In June 1939 she had moved to another state and had been unable to adjust herself to her new environment but had become nervous and homesick. She had cried frequently and tired easily. In September 1939, because of nervousness and a basal metabolic rate of  $+12$  per cent, compound solution of iodine (Lugol's solution) had been prescribed, in a dosage of 5 drops taken three times daily, from which questionable benefit had been derived. In October 1939, about eleven days before she registered at the clinic, the patient had returned to her original home. During the excitement of her reception at home she had noted difficulty in speaking; the tongue seemed to be thick and awkward. The longer she talked, the more her words would slur, so that eventually she could not be understood. Rest restored her speech temporarily. About four days prior to her coming to the clinic she had been troubled with blurred and double vision; her face felt stiff and numb most of the time, and muscular weakness had become generalized. Eating was dreaded because of difficulty in swallowing. She was at her best in the morning. By afternoon she would be exhausted. She had lost little weight.

On physical examination the patient was found to have an expressionless face but a stimulated appearance which suggested exophthalmic goiter. The skin was warm and moist. There were some edema of the eyelids, with slight bilateral ptosis of the lids and exophthalmos, and evidence of slight weakness of the right inferior oblique and inferior rectus muscles. Tremor of the fingers was moderate. Weakness of the quadriceps muscles was slight. The thyroid gland was somewhat enlarged, each lobe being about 2.5 by 5.5 cm. in size, and was firmer than normal. A systolic bruit was heard over the right lobe. The uterus was nodular and enlarged to the level of the umbilicus. The systolic blood pressure was 140 to 148 and the diastolic pressure 84 to 90, expressed in millimeters of mercury. The pulse rate was 84 beats per minute. The basal metabolic rates were  $+20$  and  $+21$  per cent. The presence of an exophthalmic goiter was strongly suspected, and compound solution of iodine was administered. After seventeen days of iodine therapy, the patient's weakness was more marked, and she presented a picture of a person suffering from extreme exhaustion. In addition, she exhibited moderate bilateral ptosis of the eyelids and marked weakness of the quadriceps muscle. Basal metabolic rates were  $+21$  and  $+23$  per cent. The basal metabolic rate as subsequently determined in the hospital was  $+10$  per cent. The patient then received an intramuscular injection of 1 mg. of prostigmine methylsulfate. Within fifteen minutes a most dramatic change occurred. She said that she felt greatly improved. The double vision and ptosis vanished; the general muscular weakness and feeling of fatigue lessened, and the thick tongue and facial numbness disappeared. She could talk and smile with ease and could walk unassisted and with confidence. She relished her supper and ate it rapidly. This feeling of exhilaration lasted about three to four hours. The next day the patient received a subcutaneous injection of sterile water, without effect. Then the injection of 1 mg. of prostigmine methylsulfate was repeated, and again marked improvement followed. Consequently, the diagnosis of myasthenia gravis of the bulbar type was established. In spite of control of the symptoms and signs of myasthenia gravis, the patient continued to

show evidences of exophthalmic goiter, the most marked of which were edema of the eyelids, a warm, moist skin and fine tremor of the fingers. These signs, the increased size and firmness of the thyroid gland and the elevated basal metabolic rate made us feel that the diagnosis of exophthalmic goiter was almost certain. Treatment with compound solution of iodine, 10 drops administered three times daily; prostigmine bromide, 9 mg. administered orally five times daily, and aminoacetic acid, 5 Gm. administered three times daily, was continued, and the patient's condition improved markedly. In December double resection of the thyroid gland was performed. Eighteen grams of thyroid tissue was removed. The thymic area was explored, but thymus tissue was not found. Pathologic examination of the thyroid tissue removed showed multiple hyaline hemorrhagic degenerating fetal and colloid adenomas in a hypertrophic parenchymatous thyroid gland.

The postoperative convalescence of the patient was uneventful, and she was dismissed fifteen days after thyroidectomy. Her general condition at that time was definitely improved. She was instructed to take daily 10 drops of compound solution of iodine, 5 Gm. of aminoacetic acid and 15 mg. of prostigmine bromide.

In April 1940 the patient returned for reexamination and consideration of surgical operation for the uterine fibromyomas. She stated that prostigmine had been needed for only two weeks after she had returned home. She had continued to take compound solution of iodine and aminoacetic acid. Her condition subjectively and objectively was satisfactory. She had gained 17 pounds (8 Kg.). At this time she said that when she became tired, the sensation was more of physiologic exhaustion than of "paralysis." The basal metabolic rate was reported to be —5 per cent. A subcutaneous injection of 1 mg. of prostigmine methylsulfate did not produce any noticeable effect. Abdominal subtotal hysterectomy was performed. The postoperative convalescence of the patient again was uneventful, and she was dismissed eighteen days after operation and was instructed to continue to take 5 drops of compound solution of iodine daily but no other medication.

At the time of her last examination at the clinic, in November 1940, the patient was able to do her own housework. She did not have any true symptoms of myasthenia gravis. Results of a general examination were essentially negative except for an increase in weight and persistent mild hypertension. The basal metabolic rate was +2 per cent. She was dismissed with advice to reduce her weight and to continue to take compound solution of iodine for several years.

In March 1941 the patient reported by letter that her health was excellent. She had lost 20 pounds (9 Kg.) by restriction of her diet.

CASE 2.—The second patient was a married woman aged 56. She registered at the clinic in July 1938, complaining chiefly of difficulty in talking and swallowing of ten months' duration. For many years she had been afflicted with nervousness, palpitation, dyspnea and tremor. In about 1933 she had noted transient episodes of mild impairment of speech and occasional regurgitation of liquids. In September 1937 speech had become persistently more difficult, and her general course had been steadily downward. She said that her tongue "wouldn't work properly." The lower jaw had become so weak that if she did not support it, the mouth would remain open constantly. She had been unable to chew foods. Swallowing would produce episodes of choking. There was loss of appetite, with an associated decrease in weight of 35 to 40 pounds (16 to 18 Kg.). Ptosis of the eyelids had occurred, and general muscular weakness had become progressive. Her general condition had been somewhat better in the mornings, but frequent rest periods were of only temporary benefit.

Physical examination revealed a stimulated, emaciated woman. Her skin was warm and moist. Moderate ptosis of the eyelids was present. The mouth remained open, and saliva drooled from it. She experienced great difficulty in talking or swallowing. Virtually all the muscles of the body were atrophied in varying degree, and there was associated loss of strength. Her gait was a slow, unsteady shuffle. The thyroid gland was low lying, and palpable portions of each lobe measured 3 by 4 cm. The systolic blood pressure varied from 166 to 190 and the diastolic pressure from 108 to 140, expressed in millimeters of mercury. The pulse rate was 112 to 118 beats per minute.

Results of routine laboratory tests were normal save for elevated basal metabolic rates, +62, +49 and +71 per cent. The favorable response of the patient to the intramuscular injection of 1 mg. of prostigmine methylsulfate was so definite that no doubt was left as to the validity of the diagnosis of myasthenia gravis. Because of the patient's history of nervousness, palpitation, dyspnea and tremor and because of the clinical picture of stimulation so characteristic of exophthalmic goiter, the enlarged thyroid gland and the elevated basal metabolic rates, the diagnosis of exophthalmic goiter was also made.

Compound solution of iodine was prescribed, 10 drops to be taken three times daily, with 3 mg. of prostigmine bromide to be taken orally five times daily. After seven days of this therapy, with rest in bed, the patient's general condition improved. She was able to talk and swallow much better than at the time of her admission. She could cough, sneeze and yawn. Another basal metabolic rate was +49 per cent. Even though the patient exhibited some general improvement as a result of medical management, the surgical risk was still prohibitive. It was feared that she would be unable to cough up mucus or to swallow; hence, thyroidectomy was not done, but roentgen therapy was substituted. At the time of her dismissal, the patient was taking 10 drops of compound solution of iodine three times daily and 6 mg. of prostigmine bromide orally five times daily.

This patient never returned for further consideration. She died at home a few months after her dismissal from the clinic.

CASE 3.—The patient was a married woman aged 25. She registered at the clinic in March 1931. She complained chiefly of ptosis of the eyelids and double vision of one and a half year's duration and of difficulty in talking and swallowing of three months' duration. She always had been "warm blooded." In 1926 she had noticed that her legs trembled and that they seemed to be about to give way when she walked much. Only once had she actually fallen to her knees. Since 1929 she had been afflicted with transient episodes of diplopia and ptosis. In 1930, three months before she came to the clinic, she had experienced difficulty in swallowing both liquids and solid foods. Regurgitation had become more frequent; talking was an effort. Prolonged speech had tended to become thick and finally had failed. Diplopia and ptosis had occurred more often. General muscular weakness progressed, and at times the patient had fallen to the floor. Usually, she had felt well in the mornings but lost strength rapidly throughout the rest of the day. Rest periods had relieved her temporarily.

General examination revealed a well developed, obese woman, with masklike facies, marked bilateral ptosis of the eyelids and varying degrees of weakness of the ocular muscles. She appeared to be stimulated, and her skin was warm and moist. Moderately fine tremor of the hands was present. There was generalized muscular weakness, with moderate weakness of the quadriceps muscle. The thyroid gland was just palpable. The systolic blood pressure varied from 110 to 124 and

the diastolic pressure from 70 to 78, expressed in millimeters of mercury. The pulse rate varied from 89 to 98 beats per minute.

Results of laboratory investigations were normal save for elevated basal metabolic rates, +22, +23 and +21 per cent. A diagnosis of myasthenia gravis was made on the basis of the history and the results of the general examination. The stimulated appearance and behavior of the patient, with the elevated basal metabolic rates, led to the suspicion of associated exophthalmic goiter.

In April 1931 administration of 10 drops of compound solution of iodine three times daily was commenced. After seven days of such therapy the basal metabolic rates had decreased to +3 and +5 per cent, and at the end of sixteen days, to -4 per cent. The patient's general course was variable but tended to be worse. It was then decided to discontinue administration of compound solution of iodine and to start administration of ephedrine sulfate in doses of  $\frac{2}{3}$  grain (0.043 Gm.) twice daily.

By May 1931, a month later, the patient's general condition was definitely improved. She still tended to tire easily. Her hands were slightly tremulous. She was disturbed by palpitation. She had lost weight slightly; yet her appetite was good. Basal metabolic rates were +21 and +17 per cent. A second course of therapy with compound solution of iodine, 10 drops given three times daily, was ordered, in conjunction with administration of  $\frac{2}{3}$  grain (0.043 Gm.) of ephedrine sulfate twice daily. After nine days of this therapy the patient's general condition was further improved, both subjectively and objectively. The basal metabolic rate decreased from +21 and +17 per cent to +3 and -2 per cent. The diagnosis of exophthalmic goiter was thus verified and thyroidectomy was advised.

The patient did not return for operation, as had been planned. It was later learned from her husband that because of increased dysphagia she had choked to death suddenly in October 1931.

CASE 4.—The patient was a married physician aged 56. He registered at the clinic in June 1935, complaining chiefly of loss of general strength and difficulty in chewing of six months' duration. The patient had felt perfectly well until January 1935, at which time he had noted that his power to chew definitely weakened after the first few bites of solid food. Such foods as meats had to be ground before he could eat them. He also had observed that his strength was normal in the mornings and that it gradually declined thereafter. Rest periods would revive him temporarily. In May 1935, three weeks before his admission to the clinic, dysphagia had occurred. He said that the "muscles of his throat didn't seem to contract" and that he had had to wash his food down with water. He thought his loss of 30 pounds (14 Kg.) of weight might have been caused by his fear of eating, for previously he had had a good appetite.

The general examination showed the patient to be normally developed but considerably overweight. He appeared to be stimulated, with skin that was warm and moist. He presented a fine type of hand tremor. The palpable portions of the thyroid gland were definitely nodular. The right lobe measured 4 by 6 cm. and the left 3 by 5 cm. Examination of the heart revealed a diastolic murmur characteristic of aortic insufficiency. The heart was of normal size and compensated. Marked sinus arrhythmia, verified by an electrocardiogram, was present. Loss of muscular strength was generalized and was of mild degree. The systolic blood pressure was 166 and the diastolic pressure was 80, expressed in millimeters of mercury. The pulse rate was 104 beats per minute.

The only positive laboratory observations were the elevated basal metabolic rates of +19 and +17 per cent and a roentgenologic shadow of undetermined

nature in the upper part of the mediastinum. A diagnosis of adenomatous goiter with hyperthyroidism was made, and myasthenia gravis was suspected.

The patient was instructed to take 10 drops of compound solution of iodine three times daily. In July 1935, one month later, he returned for reexamination. He thought he was slightly weaker than he had been at dismissal. Results of examination did not show any improvement in his condition. Administration of compound solution of iodine was discontinued, and ephedrine sulfate was prescribed,  $\frac{1}{8}$  grain (0.008 Gm.) three times daily. One level tablespoon of aminoacetic acid was to be taken five times daily. After five days of this regimen the patient could chew food more vigorously and strength returned to his arms and hands. Such a response to ephedrine sulfate substantiated the diagnosis of myasthenia gravis. At dismissal he was advised to continue to take ephedrine sulfate and aminoacetic acid.

In August 1935 reexamination showed the patient's general myasthenic state to be unchanged. Tremor of the hands had increased. The basal metabolic rate was found to be +24 per cent. The only change in the therapeutic program was the addition of potassium chloride, 1 teaspoon three times daily. Thereafter the patient kept in constant contact with the clinic, either by personal presentation or by mail. His course was variable, with the general trend definitely downward. Different therapeutic agents, such as aminoacetic acid, ephedrine sulfate, prostigmine and potassium chloride, were employed, without much success.

In March 1937 the patient gave a history of angina pectoris. In May 1937 his condition was worse. He had been troubled by a cold, and the mucus produced distressed him. Swallowing was difficult. His heart "raced," and palpitation disturbed him. The carotid vessels were seen to pulsate strongly. Attention was focused on the thyroid gland, which was believed to be overactive again. All medication was stopped, and compound solution of iodine was prescribed, 15 drops three times daily for three or four days, at the end of which time 10 drops was to be taken three times daily. After seventeen days of iodine therapy the patient's general condition was considerably improved. His strength returned, and his nervousness decreased markedly. Pulsations of the carotid vessels diminished. The patient slept better. He was permitted to return home and was advised to take compound solution of iodine daily.

In September 1937 he presented himself for the last time. He had lost considerable weight. His loss of strength was more marked. His speech and his ability to swallow were poor. At times he could not retain food introduced by tube. His breathing was laborious. The administration of prostigmine bromide was started, and the dose was increased from 15 to 30 mg. daily, with no apparent effect.

In October 1937, after an attempt had been made to feed the patient by means of a tube, he suddenly collapsed. After the intramuscular injection of 1 mg. of prostigmine methylsulfate he regained consciousness. This dose was reenforced later by the oral administration of 15 mg. of prostigmine bromide. The patient improved so remarkably that he was able to swallow nourishment and take his feeding by tube without much difficulty that same day. He died suddenly three days later, while his wife was helping him with his morning toilet.

#### COMMENT

Exophthalmic goiter and myasthenia gravis may present symptoms that are somewhat similar, although as a rule when either condition exists the other can be readily excluded. Both may occur in any decade

of life; both affect females more frequently than males. Muscular weakness is a common symptom of both. Spontaneous exacerbation and remission, with a tendency toward progression, are characteristic of both diseases. Weakness of the ocular muscles frequently is seen in both conditions, but whereas ptosis of the lids is usual in myasthenia gravis, the upper lids are often retracted in exophthalmic goiter. In both diseases the thymus body may be abnormally enlarged, although the enlargement may not be exactly similar in the two diseases.

When the two diseases exist simultaneously either one may easily be overlooked. The response to prostigmine of patients who have myasthenia gravis is dramatic and is an important diagnostic point, since patients suffering from exophthalmic goiter alone are not benefited by it. The effect of iodine on exophthalmic goiter is well known, and it may be administered as an aid in diagnosis; however, in our cases its effect alone was not consistently good, and it may be that its characteristic effect on exophthalmic goiter might not be obtained for patients who also have untreated myasthenia gravis. The basal metabolic rate may afford important information, because it is not elevated in patients suffering from uncomplicated myasthenia gravis. Garvey,<sup>3</sup> in 1930, stated that the basal metabolic rate was less than normal in the presence of myasthenia gravis. He reported basal metabolic rates of —23 and —24 per cent in 1 case of myasthenia gravis and a rate of —9 per cent in a second case. In a review of all the cases of myasthenia gravis on record at the Mayo Clinic, it was found that the basal metabolic rate had been determined in 40 cases and that in all it was within an acceptable normal range of —18 to +12 per cent. The basal metabolic rate was higher than +10 per cent in 1 case and lower than —10 per cent in 6 cases.

Pathologically, both exophthalmic goiter and myasthenia gravis are associated with significant involvement of the thymus body.<sup>3a</sup> The association of an enlarged thymus body with exophthalmic goiter was first recorded by Markham, in 1858. The incidence of a hyperplastic or hypertrophied thymus body in cases of exophthalmic goiter varies from 66 (Giordano<sup>4</sup>) to 100 per cent (Potter<sup>5</sup>). Other cited figures range between these extremes. In Giordano's survey of cases of adenomatous

3. Garvey, J. L.: Ophthalmoplegia and Graves' Disease, *Ann. Int. Med.* **3**:917-919 (March) 1930.

3a. Since this paper was written, the following important contribution has appeared: Blalock, A.; Harvey, A. M.; Ford, F. R., and Lilienthal, J. L.: The Treatment of Myasthenia Gravis by Removal of the Thymus Gland: Report of a Case, *J. A. M. A.* **117**:1529-1533 (Nov. 1) 1941.

4. Giordano, A. S.: The Frequency of Thymic Hyperplasia in Toxic and Non-Toxic Goiters, *J. Indiana M. A.* **16**:362-366 (Nov.) 1923.

5. Potter, E. B.: Persistent Thymus in Exophthalmic Goiter, in Stone, W. J.: Contributions to Medical Science Dedicated to Aldred Scott Warthin, Ann Arbor, Mich., George Wahr, 1927, pp. 205-220.

goiter with hyperthyroidism, the thymus body was found to be hyperplastic in 50 per cent of the cases, a figure which practically equals the incidence which he reported for exophthalmic goiter. Blackford and Freligh<sup>6</sup> studied carefully the observations made at necropsy on 74 patients suffering from exophthalmic goiter who had died in the course of the disease. They found a hypertrophic thymus body in all patients who were less than 40 years of age and in half of those who were more than 40 years of age. One of us (J. deJ. P.<sup>7</sup>) had the opportunity to study for a series of 7 patients suffering from exophthalmic goiter in whom hyperthyroidism had been completely controlled by partial resection the observations made at necropsy when death occurred, a year or more after partial thyroidectomy, from causes other than hyperthyroidism. Although the group was small, it appeared significant that in no case was a persistent or hypertrophic thymus body present. If it could be assumed that in some of these patients a hypertrophic thymus body had been present during the course of the hyperthyroidism, the absence of such hypertrophy after complete recovery of the patient would indicate that control of the hyperthyroidism had resulted in involution of the thymus body.

Weigert, cited by Norris,<sup>8</sup> in 1901, was the first to describe a thymic tumor associated with myasthenia gravis. Norris in 1937 brought to date his review of the literature of all cases of myasthenia gravis in which postmortem examination had been made. He found 82 such cases. In 37 cases, or 45 per cent, there were definite lesions of the thymus gland, in the nature either of hyperplasia or of a thymoma. Since 1937, 9 additional cases have been reported.<sup>9</sup> In 6 of these, lesions of the thymus body were present. The case reported by Schönberg was one of exophthalmic goiter and myasthenia gravis. Histopathologic examination of the thyroid tissue disclosed the presence of lymphocytosis and parenchymal changes "typical of Basedow's disease." Histopathologic examination of the thymus body revealed hyalinization of Hassall's

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6. Blackford, J. M., and Freligh, W. P.: The Thymus in Adults with Especial Reference to Goiter, abstracted in *Collected Papers of the Mayo Clinic*, Philadelphia, W. B. Saunders Company, 1916, vol. 8, pp. 507-512.

7. Pemberton, J. deJ.: Recurring Exophthalmic Goiter, *J. A. M. A.* **94**:1483-1489 (May 10) 1930.

8. Norris, E. H.: A Thymoma (Adenoma of the Thymus) from an Unusual Case of Myasthenia Gravis, with Observations on the General Pathology, *Am. J. Cancer* **30**:308-317 (June) 1937.

9. Barton, F. E., and Branch, C. F.: Myasthenia Gravis: Report of a Case with Necropsy, *J. A. M. A.* **109**:2044-2048 (Dec. 18) 1937. Miller, H. G.: Myasthenia Gravis and the Thymus Gland, *Arch. Path.* **29**:212-219 (Feb.) 1940. Peer, G. F., and Farinacci, C. J.: Report of Case of Myasthenia Gravis Associated with Thymoma, *Mil. Surgeon* **82**:350-355 (April) 1938. Scannell, R. C.: Myasthenia Gravis: A Case with Necropsy, *J. Iowa M. Soc.* **30**:154-159 (April) 1940. Schönberg.<sup>2e</sup>

corpuscles, hyperemia and predominance of small round cells. Neither a thymic tumor nor thymic hyperplasia was distinctly present.

A review of the records of the Mayo Clinic revealed 8 cases of myasthenia gravis in which complete necropsy except for the brain and the spinal cord had been done. In 1 case examination of the thymus body had revealed nodular hyperplasia. In a second case a malignant thymoma was found, with metastasis to the left visceral and parietal pleuras. Including these 8 cases, the recorded number of cases of myasthenia gravis in which necropsy has been done now totals 99. In 45 cases, or approximately 45 per cent, prominent anatomic lesions of the thymus body were present. The significance of this relation remains unknown, but the incidence of it is far too high to be merely coincidental.

The physiologic chemistry underlying the state of exophthalmic goiter is still in the hypothetic stage, and the nature of the muscular weakness of this disease is unknown. Presumably it is due to intrinsic chemical and/or physical changes, some of which may in part involve the phosphocreatine mechanism. Because of the role of serum choline esterase in the conduction of nerve impulses, and to ascertain whether any possible relation to the muscular weakness present in exophthalmic goiter existed, values for serum choline esterase were determined in 13 cases in which exophthalmic goiter had been untreated. In all cases the values were normal.

At present the most favored theory concerning the cause of muscular weakness in myasthenia gravis suggests faulty transmission of nerve impulses due to a defect at the myoneural junction. The exact chemical reaction is not known. Whether there is excess choline esterase or inadequate acetylcholine at the motor end plates or curare-like toxin or some other unknown factor in the neuromuscular tissues remains to be determined. In cases of combined exophthalmic goiter and myasthenia gravis it may be that the goiter serves as the precipitator of the latter disease in the patient who has a latent tendency toward its development. The other possibility is that in rare instances exophthalmic goiter may produce muscular disturbances that are identical with those occurring in cases of myasthenia gravis. The infrequency of ptosis or of weakness of the pharyngeal muscles in cases of exophthalmic goiter with extreme generalized muscular weakness and the lack of effect of prostigmine on the muscular weakness associated with exophthalmic goiter argue against the latter possibility.

The prognosis in cases of properly treated exophthalmic goiter ordinarily is good, but in cases of myasthenia gravis it is grave, particularly if the bulbar type is present. When these two conditions prevail at the same time the prognosis is extremely poor. Yet it is of interest to note that spontaneous remission may occur in a patient who



has the combined syndromes. Rennie<sup>10</sup> reported a case of such recovery; the patient presented himself in a good state of health eleven years after the diagnosis had been made. It is also of interest to note that in our cases the clinical manifestations of hyperthyroidism preceded the onset of myasthenia gravis by months to years.

Surgical treatment of exophthalmic goiter complicated by myasthenia gravis offers certain difficulties. It is important that the patient be able to cough and to swallow in order to dispose of tracheal mucus, which often appears after thyroidectomy. In the instance herein recorded in which thyroidectomy was performed, treatment with prostigmine resulted in improvement in muscular strength sufficient for us to feel no concern in this regard. An ample supply of prostigmine for parenteral use was at hand, but in the absence of any unusual postoperative reaction it was not needed.

#### SUMMARY

Three cases of exophthalmic goiter combined with myasthenia gravis of the bulbar type and 1 case of adenomatous goiter with hyperthyroidism and myasthenia gravis have been presented. In 1 of these cases subtotal thyroidectomy has been performed successfully, with relief of symptoms of both conditions.

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10. Rennie, G. E.: Exophthalmic Goitre Combined with Myasthenia Gravis, *M. J. Australia* 2:416-417 (Nov. 15) 1919.

# INTRAVENOUS USE OF SODIUM SULFADIAZINE IN THE TREATMENT OF PNEUMO- COCCIC PNEUMONIA

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In previous papers we have reported on the behavior of sulfadiazine (2-[paraaminobenzenesulfonamido]-pyridine) in normal subjects,<sup>1</sup> and its use in the treatment of pneumococcic pneumonia.<sup>2</sup> Oral therapy with sulfadiazine<sup>2</sup> was supplemented with intravenous administration of the sodium salt of sulfadiazine in certain instances when rapid elevation of the level of the drug in the blood was desired. The behavior of the drug when given by vein suggested that administration of the entire dose of sulfadiazine by the intravenous route might be advantageous. Observations on the intravenous use of sodium sulfadiazine<sup>3</sup> without oral therapy in the treatment of pneumococcic pneumonia are described in the present paper.

## MATERIAL AND METHOD

*Intravenous Administration of Sodium Sulfadiazine to Normal Subjects.*—As a guide to the therapeutic use of sodium sulfadiazine the fate of this compound administered by vein was first investigated in normal subjects (table 1). Five adult males with normal renal and hepatic function were each given 3 Gm. of sodium sulfadiazine (equivalent to 2.67 Gm. of sulfadiazine) intravenously as a

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\* David Riesman Fellow in Medicine.

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From the Committee for the Study of Pneumonia, Philadelphia General Hospital.

1. Reinhold, J. G.; Flippin, H. F.; Schwartz, L., and Domm, A. H.: The Absorption, Distribution, and Excretion of 2-Sulfanilamido Pyrimidine (Sulfapyrimidine, Sulfadiazine) in Man, *Am. J. M. Sc.* **201**:106 (Jan.) 1941.

2. Flippin, H. F.; Rose, S. B.; Schwartz, L., and Domm, A. H.: Sulfadiazine and Sulfathiazole in the Treatment of Pneumococcic Pneumonia: A Progress Report on Two Hundred Cases, *Am. J. M. Sc.* **201**:585 (April) 1941.

3. Dr. Howard Hogan, Nepera Chemical Company, Yonkers, N. Y., provided the sodium sulfadiazine used in this study.

5 per cent solution in sterile distilled water. Doses averaged 0.038 Gm. per kilogram of body weight, ranging between 0.033 and 0.045 Gm. per kilogram. The concentration of the drug in the blood and urine was determined by the method of Bratton and Marshall.<sup>4</sup> The highest concentration of free drug observed in the blood was 15 mg. per hundred cubic centimeters fifteen minutes after injection. Blood collected eight hours after the drug was given showed an average concentration of 5.4 mg. of free sulfadiazine per hundred cubic centimeters, while after twenty-four hours an average concentration of 2.5 mg. per hundred cubic centimeters remained. Comparison with the response to intravenous injection of equivalent amounts of sodium sulfathiazole (the sodium salt of 2-[paraaminobenzenesulfonamido]-thiazole)<sup>5</sup> indicates that the concentration of sulfadiazine in the blood is much more effectively maintained.

The excretion of sulfadiazine in the urine was slower than that of sulfathiazole,<sup>5</sup> an average of 74 per cent of the former as compared with 96 per cent of the latter appearing in the urine within twenty-four hours. The equivalent of 93 per

TABLE 1.—*The Fate of a Single Intravenous Dose (3 Gm.) of Sodium Sulfadiazine*

Time, Hr.	Blood *			Urine †			
	Free Drug, Mg. per 100 Cc.	Total Drug, Mg. per 100 Cc.	Acetylated Drug, per Cent	Free Drug, Mg. per 100 Cc.	Total Drug, Mg. per 100 Cc.	Acetylated Drug, per Cent	Cumulative Excretion, per Cent
¼	11.6	12.8	10.0				
½	10.9	11.9	8.4				
1	9.5	10.5	9.5				
2	8.5	9.5	10.5				
4	6.9	8.1	14.8	115	147	22	17
8	5.4	6.4	15.6	64	101	36	35
24	2.5	3.5	28.6	48	91	47	74
48	0.8	1.6	50.0	31	50	39	93

\* Average values for 5 subjects.

† Average values for 4 subjects.

cent of injected sulfadiazine was recovered in the urine within forty-eight hours. The figures for excretion are based on the assumption that all material reacting with the Bratton and Marshall reagent is unaltered drug or reacts as equivalent amounts of drug. The intravenous administration of a single 3 Gm. dose of sodium sulfadiazine did not result in any apparent untoward reaction. Our results agree with those of Peterson and associates.<sup>6</sup>

*Treatment of Subjects with Pneumonia.*—Twenty-five adult male patients with pneumonia, admitted consecutively, were treated with sodium sulfadiazine administered entirely by vein. As in previous studies, the diagnosis of pneumonia was established by clinical history, physical examination and, when indicated, by roentgenograms. A specific type of pneumococcus was obtained from the sputum or

4. Bratton, A. C., and Marshall, E. K., Jr.: A New Coupling Reagent for Sulfanilamide Determination, *J. Biol. Chem.* **128**:537 (May) 1939.

5. Reinhold, J. G.; Flippin, H. F., and Schwartz, L.: Observations on the Pharmacology and Toxicology of Sulfathiazole in Man, *Am. J. M. Sc.* **199**:393 (March) 1940.

6. Peterson, O. L.; Strauss, E.; Taylor, F. H. L., and Finland, M.: Absorption, Excretion, and Distribution of Sulfadiazine (2-Sulfanilamido-Pyrimidine), *Am. J. M. Sc.* **201**:357 (March) 1941.

the blood in all but 4 instances, and in these the pneumococci in the sputum failed to yield a type with pneumococcus serums types I to XXXIII. Repeated blood counts and daily urinalyses were made on all patients. Concentrations of free and total drug in the blood were determined for samples collected twelve hours after the preceding injection of the drug and immediately before the next injection. Other laboratory studies were performed as indicated.

*Dosage of Sodium Sulfadiazine.*—In order to make the conditions of this study as uniform as possible and to facilitate the collection of samples of blood and the administration of the drug, we employed the following routine: With the exception of the initial dose, sodium sulfadiazine was injected at 9 a. m. and 9 p. m. Patients admitted before 5 a. m. or 5 p. m. received the usual initial 2 to 3 Gm. dose of drug as soon as possible and were then placed on the routine dose schedule. Those admitted after 5 a. m. or 5 p. m. were given a somewhat larger initial dose (see next paragraph), depending on the time of admission, and were placed on the regular regimen twelve to sixteen hours later. Thus most of the patients received medication at the same time, day and night. Sodium sulfadiazine was administered intravenously as a 5 per cent solution in sterile distilled water, from a syringe equipped with a 21 gage needle. If a needle of this caliber is used there is little danger of introducing the solution too rapidly into the vein. Care was taken to avoid escape of the material into the tissues of the arm.

The first 8 patients in this study received an initial intravenous injection of 3 to 4 Gm. of sodium sulfadiazine, depending on the time of admission, followed by 3 Gm. every twelve hours, day and night. Treatment was continued until the temperature remained normal for thirty-six to forty-eight hours and there was evidence of clinical improvement. For the remaining 17 patients the same dose schedule was followed, except that smaller amounts (2 Gm.) of the drug were employed. The average total dose for patients receiving 3 Gm. was 26.5 Gm., as compared with 18 Gm. for those receiving the 2 Gm. dose. Of the 25 patients included in this report, 4 received type-specific serum in addition to the drug.

#### THERAPEUTIC RESULTS

In this report we have included every patient with a diagnosis of pneumonia who received drug therapy, regardless of complications or length of stay in the hospital. The relevant data concerning these patients are given in table 2. Of the 25 patients with pneumonia, 4 died. Cultures of blood from 7 (28 per cent) of the patients were positive for pneumococci; 3 of the 7 died. All of the patients who died represented extremely poor therapeutic risks. There is no significant difference in mortality rate with the use of smaller (2 Gm.) amounts of sodium sulfadiazine than with larger (3 Gm.) doses.

*Influence of Treatment on Course of the Disease.*—A critical drop in body temperature occurred in 14 patients within twenty-four hours and in 18 by the end of forty-eight hours. This agrees closely with the temperature response to oral therapy with sulfadiazine. The temperature fell and remained normal within twenty-four hours in only 2 instances and within forty-eight hours in 4 cases. In this respect the oral administration of sulfadiazine<sup>2</sup> gave more satisfactory results.

TABLE 2.—Summary of Data for Twenty-Five Patients with Pneumococcal Pneumonia Treated with Sodium Sulfadiazine Administered Intravenously

Patient	Age, Years	Treatment Begun, Day of Disease	Lobe Affected *	Type of Pneumococcus	Blood Culture	Sodium Sulfadiazine		Type-Specific Antipneumococcus Serum, Units	Toxicity	Response	Comment
						Total Dose, Gm.	No. of Injections				
1	37	10	RL	IV	Negative	25	8	.....	Crystalluria	Good	
2	35	3	LL	VII	Negative	25	8	.....	.....	Good	
3	23	3	RL	I	Negative	31	10	.....	.....	Fair	Sterile pleural effusion
4	61	1	LU; LL	XXIX	Negative	24	8	.....	Crystalluria, occasional red blood cells	Good	Diabetes mellitus
5	39	2	LU	XIX	Negative	28	9	.....	Crystalluria, occasional red blood cells	Good	
6	72	4	RU; RM; RL	III	Positive	7	2	.....	.....	Death	Moribund on admission; no autopsy
7	62	6	RU; RL	...	Negative	28	9	.....	.....	Death	Degenerative heart disease with progressive failure; no autopsy
8	34	6	RU; RM; RL; LU; LL	IV	Positive	10	4	100,000	.....	Death	Leukopenia (white cell count 3,000) on admission; autopsy: lobar pneumonia involving all lobes
9	14	3	RL	XX	Negative	15	7	.....	Vomited once	Good	
10	33	6	RU; RM; RL	XIV	Negative	26	13	240,000	Psychosis	Fair	
11	49	2	RL	II	Negative	17	8	.....	Vomited once	Good	
12	29	1	RL	I	Negative	18	8	.....	.....	Good	
13	72	2	RL	III	Positive	24	11	100,000	.....	Fair	
14	22	2	RL	XII	Negative	19	9	.....	.....	Good	
15	34	6	RU	VIII	Positive	18	8	.....	.....	Good	
16	48	7	LU; LL	...	Negative	13	6	.....	.....	Good	
17	34	1	RM; RL	...	Negative	20	9	.....	.....	Good	
18	38	2	RL	V	Positive	18	8	.....	.....	Good	
19	40	2	RL	...	Negative	22	10	.....	.....	Good	
20	43	2	LL	I	Negative	14	6	.....	Crystalluria	Good	Acute alcoholism
21	39	3	LL	XI	Negative	22	10	.....	.....	Good	
22	45	2	RL	VIII	Positive	18	8	.....	.....	Fair	
23	55	10	RU	I	Positive	20	9	500,000	.....	Good	
24	28	4	RU; RM	VIII	Negative	16	7	.....	.....	Death	Autopsy: lobar pneumonia involving upper lobe of right lung, acute bacterial endocarditis
25	63	3	RL; LL	II	Negative	19	9	.....	.....	Good	

\* The affected lobes of the lungs are designated by the following abbreviations: RU, upper lobe of the right lung; RM, middle lobe of the right lung; RL, lower lobe of the right lung; LU, upper lobe of the left lung, and LL, lower lobe of the left lung.

However, it should be pointed out that in this series the persisting elevation in temperature, following the critical fall, represented a low grade fever (99 to 100 F). A return to normal temperature within forty-eight hours has constituted one of the outstanding features of therapy with sulfanilamide or one of its derivatives in cases of pneumonia but is actually less important than the improvement in the patient's general condition. As shown in table 2, the therapeutic response in those patients who recovered was designated as good or fair. For 17 patients the results were good, and for 4 they were fair. There was no difference in temperature or therapeutic response of patients receiving 3 Gm. or those receiving 2 Gm. doses of the drug.

*Complications.*—The number of patients in this series is too small to permit evaluation of the incidence or significance of complications (table 2). Individual cases of massive pleural effusion and acute bacterial endocarditis constituted the only complications observed.

*Toxicity.*—The toxic reactions encountered in the course of this study are shown in table 2. Vomiting occurred in 2 cases but only once in each. In 1, vomiting followed immediately the injection of the drug, and this we believe was due to too rapid administration through an 18 gage needle. The other patient vomited on the third day of treatment after a rather large meal. The low incidence of vomiting in this series is comparable to that observed with the oral administration of sulfadiazine in the treatment of pneumonia.<sup>2</sup>

Crystals in small numbers, presumably of sulfadiazine, were observed in the urine of 4 patients. In 2 instances the crystals were accompanied by red blood cells, also in small numbers. A single patient showed definite evidence of a psychosis, which may have been caused by the drug.

*Blood Levels.*—Past experience with the use of sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine<sup>7</sup>) and sulfathiazole<sup>8</sup> has failed to show any definite correlation between the therapeutic effectiveness of these drugs and the concentration of free drug in the blood. Therefore, the schedule of doses which we have employed in this study is empiric. Experience with sulfadiazine and other derivatives of sulfanilamide indicates that a blood level of free sulfadiazine of 5 mg. per hundred cubic centimeters is therapeutically effective in the treatment of pneumonia. Future work may show that lower concentrations are

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8. Flippin, H. F.; Reinhold, J. G., and Schwartz, L.: Sulfapyridine and Sulfathiazole Therapy in Pneumococcic Pneumonia, *J. A. M. A.* **116**:683 (Feb. 22) 1941.

equally effective. As indicated in table 3, an average blood level of free sulfadiazine of 11 mg. per hundred cubic centimeters was obtained when 3 Gm. of sodium sulfadiazine was administered intravenously every twelve hours. In the blood of those patients receiving 2 Gm. doses, the average concentration of free drug was 6.1 mg. per hundred cubic centimeters. The lowest average level observed with the smaller dose at any one time was 4.8 mg. per hundred cubic centimeters, and this was reached twelve hours after the last injection; so the 2 Gm. dose is sufficient for effective treatment of pneumonia. In this connection it is of interest to note that the blood levels are consistently higher during the height of illness than during the last two days of therapy. This, we believe, is a result of the impaired renal function caused by

TABLE 3.—*Effect of Repeated Intravenous Administration of Sodium Sulfadiazine* \*

Dose	3 Gm. Every 12 Hr.†			2 Gm. Every 12 Hr.‡		
	Free Drug, Mg. per 100 Cc.	Total Drug, Mg. per 100 Cc.	Acetylated Drug, per Cent	Free Drug, Mg. per 100 Cc.	Total Drug, Mg. per 100 Cc.	Acetylated Drug, per Cent
2.....	8.8	10.1	12.9	7.5	8.6	12.8
3.....	10.1	11.6	12.9	7.7	8.7	11.5
4.....	11.5	12.8	10.1	6.8	7.9	13.9
5.....	13.3	14.9	10.7	6.2	7.1	12.7
6.....	12.7	13.9	8.6	6.0	6.7	10.4
7.....	12.1	13.4	9.7	5.3	6.0	11.7
8.....	10.9	12.1	9.9	5.5	6.2	11.3
9.....	8.6	9.9	13.1	5.0	5.9	15.2
10.....	...	...	....	4.8	5.4	11.1
Average.....	11.0	12.3	10.6	6.1	6.9	11.6

\* A sample of blood was collected twelve hours after each dose.

† Average values for 8 patients.

‡ Average values for 17 patients.

the infectious process before it has been brought under control of the drug. Studies on urinary output and nitrogen retention<sup>8</sup> lend support to this view. Concentration of acetylsulfadiazine remained low.

#### COMMENT

Sodium sulfadiazine administered intravenously is an effective therapeutic agent in the treatment of pneumonia and may be used with a satisfactory margin of safety to the patient. This form of therapy is offered not as a routine procedure but as a method of treatment which may be resorted to in cases in which oral therapy is impracticable or impossible. Further experience may show that smaller doses or longer intervals between injections may be substituted for those employed in this study without sacrifice of therapeutic effectiveness.

## SUMMARY

In normal subjects 3 Gm. of sodium sulfadiazine administered by vein maintained an average concentration of free drug in the blood above 5 mg. per hundred cubic centimeters for eight hours. In patients with pneumonia 2 Gm. at twelve hour intervals maintained an average concentration above 5 mg. per hundred cubic centimeters, while 3 Gm. maintained an average concentration above 8 mg. per hundred cubic centimeters.

Sodium sulfadiazine administered by vein at twelve hour intervals is an effective method for treatment of pneumococcic pneumonia. Results are comparable to those obtained by oral therapy with sulfadiazine.

Administration of sodium sulfadiazine by vein appears to be a safe procedure.

Technical assistance was given by Miss Shlomith Bethlahmy and Miss Beatrice Doak, who were detailed for this and related studies on pneumonia by the Pennsylvania State Department of Health, Division of Pneumonia Control.



# INFECTIOUS NEURONITIS

## REVIEW OF LITERATURE AND PRESENTATION OF FOUR CASES

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Since the first World War an apparently infectious form of generalized neuronitis has come to be recognized as a distinct clinical entity. It is characterized by an ascending paralysis which usually begins in the lower limbs and often involves the facial muscles, by a normal cell count and an increase in protein in the spinal fluid and by complete recovery in a large proportion of cases. A description which probably applies to this disease was given by Osler,<sup>1</sup> in 1892, under the name of "acute febrile polyneuritis." Guillain, Barré and Strohl,<sup>2</sup> in 1916, described a series of cases, and the term Guillain-Barré syndrome has been used by many writers since that time. Other terms which have been used are polyradiculoneuritis,<sup>3</sup> infective polyneuritis,<sup>4</sup> infective neuronitis,<sup>5</sup> radiculoneuritis with acellular hyperalbuminosis of the cerebrospinal fluid<sup>6</sup> and acute benign infectious myelitis.<sup>7</sup>

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1. Osler, W.: Principles and Practice of Medicine, New York, D. Appleton and Company, 1892, p. 777.

2. Guillain, G.; Barré, J. A., and Strohl, A.: Sur un syndrome de radiculonévrite avec hyperalbuminose du liquide céphalorachidien sans réaction cellulaire, Bull. et mém. Soc. méd. d. hôp. de Paris **40**:1462 (Oct. 13) 1916.

3. (a) Barker, L. F.: Acute Diffuse (Cerebral and Spinal) Polyradiculoneuritis Following Oral Sepsis, Arch. Neurol. & Psychiat. **31**:837 (April) 1934. (b) Madigan, P. S., and Marietta, S. U.: Polyradiculoneuritis, Ann. Int. Med. **12**:719 (Nov.) 1938. (c) Stone, T., and Aldrich, K.: Acute Polyradiculoneuritis, J. A. M. A. **114**:2196 (June 1) 1940.

4. (a) Bradford, J. R.; Bashford, E. F., and Wilson, J. A.: Acute Infective Polyneuritis, Quart. J. Med. **12**:88 (Oct.) 1918. (b) Pinckney, C.: Acute Infective Polyneuritis, Brit. M. J. **2**:333 (Aug. 15) 1936.

5. (a) Jacobi, H. G.: Infective Neuronitis, Arch. Int. Med. **48**:764 (Nov., pt. 1) 1931. (b) Kennedy, F.: Infective Neuronitis, Arch. Neurol. & Psychiat. **2**:621 (Dec.) 1919. (c) McIntyre, H. D.: Infective Neuronitis, Ohio State M. J. **33**:815 (Aug.) 1937.

6. Guillain, G.: Radiculoneuritis with Acellular Hyperalbuminosis of the Cerebrospinal Fluid, Arch. Neurol. & Psychiat. **36**:975 (Nov.) 1936.

7. Sands, I. J.: Acute Benign Infectious Myelitis, J. A. M. A. **96**:23 (Jan. 3) 1931.

The term neuritis has been defined by Cobb and Coggeshall<sup>8</sup> as a "degenerative (often inflammatory) process in any part of the peripheral neuron." It has thus been used as a general term, covering involvement of the nerve cell, nerve root or peripheral process. Inasmuch as the cell body or the peripheral process is seldom involved alone, without some effect on the other, it may be more accurate to use the term neuronitis, introduced by Mills<sup>9</sup> to designate involvement of the entire neuron.

#### ETIOLOGY

In his early description, Osler remarked that the onset of this disease resembles that of an acute infectious disease. Certainly the frequency with which general symptoms precede the attack is strongly suggestive of an infectious etiologic agent. In 49 of the 122 cases in the literature reviewed here there was a history of preceding illness, such as coryza, aches and pains and gastrointestinal disturbance. In all 4 of the cases reported here the patients told of antecedent infection of the upper respiratory tract or general aches and pains.

The etiologic agent has not been identified but is generally thought to be a virus. Cobb and Coggeshall<sup>8</sup> stated that in the few cases in which necropsy has been done the changes in the central nervous system have suggested a virus as the etiologic agent.

In about 70 per cent of the cases the disease has occurred in persons between the ages of 20 and 50 years, but extremes of age have been reported. About 25 per cent of patients have been under 20 and 5 per cent over 50 years. The ages of the patients in our own series were 16, 20, 50 and 52 years. In the reported cases in which sex was mentioned, approximately 60 per cent of the patients were male. In the cases reported here, 2 patients were male and 2 were female.

#### CLINICAL COURSE

As already pointed out, the onset is often attended by coryza, aches and pains and gastrointestinal disturbances. Of the cases reviewed, such preceding illness was recorded for 31 per cent; in the remainder, the disease was first evidenced in most cases by motor symptoms, including paralysis of the extremities, loss of sphincter control and disturbance of reflexes. Sensory disturbances were experienced in approximately 50 per cent of cases.

Table 1 lists some of the commonest clinical findings in the cases reviewed. One must bear in mind that many authors were not definite in their presentation of symptoms and findings.

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8. Cobb, S., and Coggeshall, H. C.: Neuritis, *J. A. M. A.* **103**:1608 (Nov. 24) 1934.

9. Mills, C. K.: The Reclassification of Some Organic Nervous Diseases on the Basis of the Neuron, *J. A. M. A.* **31**:11 (July 2) 1898.

TABLE 1.—*Clinical Findings and Mortality*\*

Author	Number of Cases	Previous Illness	Fever	Facial Paralysis	Palsy of Other Cranial Nerves	Paralysis of Sphincters	Paralysis of Extremities	Loss of Deep Reflexes	Loss of Abdominal Reflexes	Sensory Disturbance	Number of Deaths
Barker <sup>3a</sup>	1	0	1	1	1	0	1	Diminished	0	1	0
Bradford, Bashford and Wilson <sup>4a</sup>	30	?	?	?	?	?	?	?	?	?	8
Casamajor <sup>10</sup>	2	1	1	1	0	0	2	1	1	0	2
Casamajor, L., and Alpert, G. R.: Am. J. Dis. Child. 61:99 (Jan.) 1941	3	1	1	1	0	0	3	3	?	1	0
Fox and O'Connor (present series)	4	3	0	1	0	1	4	4	2	2	1
Glavin, Moersch and Kernohan <sup>11</sup>	20	13	0	7	0	0	0	18	20	15	5
Guillain <sup>a</sup>	10	0	0	2	1	2	7	8	10	10	0
Holmes <sup>12</sup>	12	?	?	?	?	?	?	?	?	?	2
Kennedy <sup>5b</sup>	4	4	3	4	2	3	3	3	1	2	1
Madigan and Marietta <sup>3b</sup>	1	0	1	1	1	0	1	1	1	1	0
McIntyre <sup>5c</sup>	7	2	0	5	4	2	4	5	5	6	2
Pinekney <sup>4b</sup>	5	3	0	2	3	1	2	3	4	2	1
Strauss, I., and Rabiner, A.: Arch. Neurol. & Psychiat. 23:240 (Feb.) 1930	7	4	2	0	1	3	1	4	4	6	0
Stone and Aldrich <sup>3c</sup>	2	1	0	2	1	0	2	1	1	2	0
Taylor, E. W., and McDonald, C. A.: Arch. Neurol. & Psychiat. 27:79 (Jan.) 1932	16	8	3	16	3	5	5	11	10	12	3
Viets, H. R.: Arch. Neurol. & Psychiat. 17:704 (June) 1927	2	1	1	1	0	1	1	2	1	2	1
Totals	126	41	13	42	17	18	39	65	60	62	26

\* It should be noted that except for the numbers of cases and numbers of deaths, data for the series of Bradford and associates and of Holmes (a total of 42 cases) are not included in this table.

Disturbances of motor function are the most striking evidence of the disease. Fatigue and muscular weakness, most pronounced in the extremities, are frequently present in the early stage. A few patients show no such preliminary weakness but pass directly into the paralytic phase: A patient may suddenly find himself unable to rise from a sitting position or may begin to stumble as he walks. The affected muscles are flaccid but seldom show wasting. According to Pinckney,<sup>4b</sup> reflexes are sometimes surprisingly obtained when voluntary power is almost absent. Pinckney also stated that the paralysis is sometimes greater in the proximal than in the peripheral portions of the limbs. The paralysis usually involves both sides, though not necessarily equally. The upper limbs are usually involved after the lower. The intercostal muscles and the diaphragm are seldom involved. As shown in table 1, abdominal and deep reflexes are abolished in about 50 per cent of the cases. This is usually noticeable in the early stages of the disease and is sometimes the only evidence of nerve damage. In about 35 per cent of the cases facial paralysis is apparent; when it occurs, it follows paralysis of the limbs. In 13 per cent of the cases other cranial nerves are involved; palsies of the cranial nerves appear as diplopia, nystagmus, lingual deviation, dysphagia and aphasia.

Sensory disturbances are neither constant nor characteristic. In about 50 per cent of the cases the patients complained of sudden pain, paresthesia or anesthesia.

The prognosis in this disease is usually good. As indicated in table 1, the mortality in the literature reviewed was approximately 20 per cent; it should be noted that in 10 cases death occurred in wartime, when other hazards may have been somewhat greater than those encountered in civilian practice. The paralysis in the survivors commonly disappeared within two or three months; in 3 of our cases paralysis disappeared within a few days. Bradford and associates<sup>4a</sup> stated that six months' convalescence was usually necessary before a patient could return to his duties. The process of recovery occurs in opposite order from that of development of paralysis; i. e., the arms usually regain their normal tonus before the legs. It has been noted in a few cases that deep tendon reflexes were slow in returning and have occasionally been absent for years after apparent recovery from the disease.

#### LABORATORY FINDINGS

Blood studies offer little of significance in cases of this disease. According to Bradford and co-workers, there may be a moderate leukocytosis, but total red cell, total white cell and differential counts are normal. Examination of cerebrospinal fluid is of the greatest importance; the significant findings are a marked elevation of protein and a normal number (or total absence) of cells. This is the so-called albu-

minocytologic dissociation. Guillain stated that unless the cerebrospinal fluid protein exceeds 300 mg. per hundred cubic centimeters, a case does not belong to this syndrome.

The results of examinations of cerebrospinal fluid recorded in the literature reviewed here are shown in table 2. In 55 cases (made up largely of the wartime groups of Bradford and associates, Holmes and Kennedy), spinal fluid protein was not mentioned. Among the others, however, significant increase in protein was observed in 56 cases. In 85 cases the cell count was within normal limits; in 25 cases this important point was not mentioned.

TABLE 2.—*Results of Examination of Spinal Fluid*

	Number of Cases	Number of Instances of Normal Cells	Number of Instances of Increased Protein
Barker <sup>3a</sup> .....	1	1	1
Bradford, Bashford and Wilson <sup>4a</sup> .....	30	30	?
Casamajor <sup>10</sup> .....	2	?	?
Fox and O'Connor (present series).....	4	4	4
Gilpin, Moersch and Kernohan <sup>11</sup> .....	20	18	20
Guillain <sup>6</sup> .....	10	10	9
Holmes <sup>12</sup> .....	12	?	?
Kennedy <sup>5b</sup> .....	4	?	?
Madigan and Marletta <sup>3b</sup> .....	1	1	1
McIntyre <sup>5c</sup> .....	7	7	7
Pinckney <sup>4b</sup> .....	5	4	4
Strauss, I., and Rabiner, A.: Arch. Neurol. & Psychiat. <b>23</b> : 240 (Feb.) 1930.....	7	?	?
Taylor, E. W., and McDonald, O. A.: Arch. Neurol. & Psychiat. <b>27</b> : 79 (Jan.) 1932....	16	4	4
Viets, H. R.: Arch. Neurol. & Psychiat. <b>17</b> : 794 (June) 1927.....	2	1	1
Casamajor, L., and Alpert, G. R.: Am. J. Dis. Child. <b>61</b> : 99 (Jan.) 1941.....	3	3	3
Stone and Aldrich <sup>3c</sup> .....	2	2	2
Totals.....	126	85	56

Stone and Aldrich <sup>3c</sup> pointed out that the elevation of protein may not be apparent at the first examination; in 1 of their cases it was first observed on the seventh day of the disease and in another on the fourteenth day. Once hyperalbuminosis of the cerebrospinal fluid develops, it is likely to persist through convalescence.

#### DIFFERENTIAL DIAGNOSIS

It is important, of course, to differentiate this disease from poliomyelitis. Albuminocytologic dissociation may occur rarely in cases of poliomyelitis, but the protein is not likely to reach the high levels encountered in cases of infectious neuronitis. If the paralysis involves the intercostal muscles, the disease is probably not infectious neuronitis.

Postdiphtheritic polyneuritis may cause a similar increase in cerebrospinal fluid protein but may usually be identified by smears and cultures

of nose and throat. Syphilis may occasionally give rise to acellular hyperalbuminosis, but it may be recognized by the history and by the positive Wasserman reaction of the blood or the spinal fluid.

Muscular atrophies and dystrophies do not usually cause any abnormality of the cerebrospinal fluid; in instances in which the protein is elevated, it seldom exceeds 100 mg. per hundred cubic centimeters. Tumor of the spinal cord may be recognized by altered pressure relations and frequently by localizing sensory and motor changes.

Alcoholic neuritis is usually accompanied by edema and vasomotor symptoms; in cases of such disease, moreover, the patients have a history of alcoholism and faulty diet. Lead neuritis is usually associated with severe gastrointestinal symptoms and shows a localization of motor disturbance in the extensor muscles of the hand and forearm.

#### PATHOLOGY

Inasmuch as fatalities in cases of this disease have been relatively few, pathologic investigation has not been extensive. In gross examination of specimens in 6 cases of fatal infectious neuronitis Bradford, Bashford and Wilson <sup>4a</sup> found edema of the brain and the spinal cord and a few petechial hemorrhages. Microscopically, they found degeneration of the cells of the anterior and posterior horns. In the peripheral nerves there were wallerian degeneration and proliferation of cells about the sheath of Schwann; these changes were more marked in motor than in sensory nerves and more pronounced in nerves of the lower than in those of the upper extremities. Casamajor <sup>10</sup> noted an increase of cellular neuroglia in the central gray matter, around root fibers and in the posterior root ganglions.

Gilpin, Moersch and Kernohan <sup>11</sup> studied 3 cases in which they found degenerative changes limited to the peripheral nerves. They observed proliferation of the cells of the sheath of Schwann, patchy destruction of the myelin sheaths and active degeneration of the axis-cylinders; there was marked edema of the supporting tissues. Holmes <sup>12</sup> reported similar changes in 2 fatal cases.

#### REPORT OF CASES

CASE 1.—A man aged 20 first became ill eleven days before admission to the hospital, at which time he had an infection of the upper respiratory tract and complained of some dizziness. During the following week he had pain in his knees, ankles and right wrist and was irritable. Four days before admission he had beginning paralysis of the legs.

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10. Casamajor, L.: Acute Ascending Paralysis Among Troops: Pathologic Findings, *Arch. Neurol. & Psychiat.* **2**:605 (Dec.) 1919.

11. Gilpin, S. F.; Moersch, F. P., and Kernohan, J. W.: Polyneuritis (a Group Referred to as Neuronitis), *Arch. Neurol. & Psychiat.* **35**:937 (May) 1936.

12. Holmes, G.: Acute Febrile Polyneuritis, *Brit. M. J.* **2**:37 (July 14) 1917.

*Physical Examination.*—The man was well developed, apparently well nourished and in good spirits. He was unable to sit up in bed or flex his knees, ankles or right wrist. There were hyperesthesia and pain over the right wrist and partial flaccid paralysis of the flexor muscles of the knees, thighs and arms. The reflexes were all active except the achilles, which was absent. The pharynx was injected. The chest and abdomen were normal. The temperature at admission was 100 F.

*Laboratory Findings.*—Leukocytes numbered 10,500 per cubic millimeter. A differential count showed 75 per cent polymorphonuclear cells, 21 per cent lymphocytes, 3 per cent monocytes and 1 per cent basophils. The urine was normal. The spinal fluid showed 5 cells per cubic millimeter, 332 mg. of protein, 712 mg. of chlorides and 85 mg. of sugar per hundred cubic centimeters and a negative Kahn reaction.

*Course of Illness.*—The temperature rose to 101.4 F. on the second day of hospitalization but declined to normal on the fifth day. Treatment was symptomatic, and the patient's condition gradually improved. On the sixth day after his admission, his paralysis had greatly subsided and there was no muscle tenderness; he was then permitted to go to his home, where he recovered completely from his paralysis.

CASE 2.—A girl aged 16 first became ill eleven days before admission to the hospital, when she began to complain of generalized aches and pains and tingling sensations in her toes and fingers. There was no fever, cough or coryza. Three days before admission she began to lose the use of her lower extremities, and a noticeable weakness began to develop in her upper extremities. The condition became worse, with progressive paralysis of the lower extremities and the onset of pain in the lumbar portion of the back.

*Physical Examination.*—The patient was well developed and apparently well nourished. She lay quietly in bed, unable to raise her lower extremities. Her face was flushed, and there was beginning paralysis on the right side of the face. She was able to move her arms only slightly. There was no rigidity of the neck. The tongue was red and the pharynx injected. The chest and abdomen were normal. The strength of the grasp was diminished in both hands. The extensor muscles of the arms and the flexor muscles of the legs were exceedingly weak; the flexor muscles of the arms and the extensor muscles of the legs were only slightly stronger. The biceps reflexes were diminished; the triceps, patellar and achilles reflexes were absent. Babinski and Kernig signs could not be elicited. Position sense was diminished in the lower extremities, but sensations were otherwise normal.

*Progress.*—The patient remained in the hospital for only two days, during which time the diagnosis of infectious neuronitis was made. During this time the temperature remained normal and the treatment was symptomatic. At the time she was discharged to her home her condition was essentially unchanged except that the paralysis was slightly increased. In the first week at home the patient began to regain some muscular function, and by the end of four weeks the paralysis had disappeared entirely.

*Laboratory Findings.*—The leukocyte count at admission was 11,500 per cubic millimeter. The hemoglobin concentration was 80 per cent. The spinal fluid contained 6 cells per cubic millimeter and 365 mg. of protein, 743 mg. of chlorides and 40 mg. of sugar per hundred cubic centimeters. No organisms could be demonstrated in the spinal fluid by smear or culture.

CASE 3.—A man aged 50 had a sore throat lasting eight days about four weeks before admission to the hospital. The day after recovery from his sore throat, he noticed a tingling sensation in his toes and a sense of numbness from his waist down. Two days later a steppage gait developed. The severity of the symptoms increased until it was impossible to walk. The previous medical history added nothing of significance.

*Physical Examination.*—The patient was well developed, evidently well nourished and not in apparent discomfort. The pupils were both slightly irregular and reacted sluggishly to light and distance. The pharynx was slightly injected. The chest was normal. The upper extremities were normal. There was no muscle or tendon tenderness of the lower extremities, and the paralysis apparently had disappeared entirely. There was loss of vibratory sense in the lower extremities, pelvis and spine up to the fifth thoracic vertebra. The senses of pain, light touch and temperature were not impaired. Tendon, abdominal and cremasteric reflexes were absent. The Babinski reaction could not be elicited; the gait had a slight steppage quality.

*Progress.*—The patient was in the hospital only three days, until the diagnosis of infectious neuronitis had been established. During this time he had no fever, and his symptoms remained unchanged. He was able to walk out of the hospital, and his steppage gait disappeared in the following month.

*Laboratory Findings.*—At the time of the patient's admission to the hospital the urine was normal. The red cell count was 4,980,000 and the leukocyte count 8,150 per cubic millimeter. The differential count was normal. The Wassermann and Kline reactions were negative. The blood contained 29 mg. of nonprotein nitrogen and 5.8 Gm. of total protein per hundred cubic centimeters, and the albumin-globulin ratio was 3.2:2. The spinal fluid showed 3 cells per cubic millimeter and 660 mg. of protein per hundred cubic centimeters. The Wassermann and Kline reactions of the spinal fluid were negative, as were cultures and smears for organisms. The spinal fluid contained 92 mg. of sugar and 686 mg. of chlorides per hundred cubic centimeters. Roentgenograms of the dorsal and lumbar portions of the spine were essentially normal.

CASE 4.—A woman aged 52 became ill on Jan. 22, 1941, with severe cramplike pains all over her body, headache and backache. She did not experience nausea or vomiting, and there was no history of chills or fever.

*Physical Examination.*—On January 23 the pharynx was slightly injected, and the chest and abdomen were normal. There was muscle tenderness in both legs but no rigidity. The tendon reflexes were diminished.

*Progress.*—The patient was given the usual treatment for grip. On January 26 severe pains, numbness and flaccid paralysis occurred in both legs, and the reflexes of the legs and abdomen were completely absent. On January 27 the patient was transferred to a hospital, and one of us (M. J. F.) was called in consultation; on the same day palsy of the right side of the face became apparent, as well as paralysis of the urethral and rectal sphincters. On January 30 both arms began to show some weakness. During the following week there was no further progression of paralysis, but extensive bronchopneumonia developed, which did not respond to treatment. The patient died on February 5. Unfortunately permission for autopsy was refused.

*Laboratory Findings.*—Examination of the spinal fluid on January 27 showed 1 cell per cubic millimeter and a total protein content of 156 mg. per hundred



cubic centimeters. It contained 731 mg. of chlorides and 88 mg. of sugar per hundred cubic centimeters, and the Kolmer reaction was negative.

#### COMMENT

The first 3 cases presented here demonstrate the favorable progress and complete recovery seen in a large proportion of the cases of infectious neuronitis. It would have been enlightening to ascertain the extent and the exact nature of the complications in case 4 through an autopsy.

#### SUMMARY

1. The literature on infectious neuronitis is reviewed.
2. The syndrome is characterized as follows: Previous illness occurs in about 50 per cent of the cases, with an associated ascending paralysis; acellular hyperalbuminosis of the spinal fluid is of great importance in establishing a diagnosis. The facial nerve is involved in about 35 per cent of the cases, and sensory changes may or may not be present.
3. Four cases of this disease, with a satisfactory recovery in 3, are described. In the fourth case the patient died of complicating bronchopneumonia; permission for autopsy was refused.

30334.

# SERUM PROTEINS IN CIRRHOSIS OF THE LIVER

## I. RELATION TO PROGNOSIS AND TO FORMATION OF ASCITES

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Filinski<sup>1</sup> reported that in diseases of the liver, such as cirrhosis, catarrhal jaundice, amyloidosis and carcinomatosis from primary carcinoma of the bile duct, the albumin-globulin ratio of the serum was reversed. He concluded that the alterations in serum protein values were due to pathologic changes in the liver. In many subsequent reports containing single observations on the serum proteins of patients with cirrhosis of the liver, authors<sup>2</sup> agreed that the albumin-globulin

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1. Filinski, W.: L'augmentation du taux de la globuline dans le sérum du sang comme résultat de l'insuffisance hépatique, *Presse méd.* **30**:236, 1922.

2. (a) Salvesen, H. A.: Variations in Plasma Proteins in Nonrenal Conditions, *Acta med. Scandinav.* **72**:113, 1929. (b) Abrami, P., and Wallich, R.: Modifications du sérum sanguin du foie avec ascites: Inversion du rapport sérines-globulines, *Compt. rend. Soc. de biol.* **101**:291, 1929. (c) Wiener, H. J., and Wiener, R. E.: Plasma Proteins, *Arch. Int. Med.* **46**:236 (Aug.) 1930. (d) Peters, J. P., and Eisenman, A. J.: The Serum Proteins in Diseases Not Primarily Affecting the Cardiovascular System or Kidneys, *Am. J. M. Sc.* **186**:808, 1933. (e) Snell, A. M.: The Effects of Chronic Disease of the Liver on the Composition and Physiochemical Properties of Blood: Changes in the Serum Proteins; Reduction in the Oxygen Saturation of the Arterial Blood, *Ann. Int. Med.* **9**:690, 1935. (f) Myers, W. K., and Keefer, C. S.: Relation of Plasma Proteins to Ascites and Edema in Cirrhosis of the Liver, *Arch. Int. Med.* **55**:349 (March) 1935. (g) Tumen, H., and Bockus, H. L.: Clinical Significance of Serum Proteins in Hepatic Diseases Compared with Other Liver Function Tests, *Am. J. M. Sc.* **193**:788, 1937. (h) Foley, E. F.; Keeton, R. W.; Kendrick, A. B., and Darling, D.: Alterations of Serum Proteins as Index of Hepatic Failure, *Arch. Int. Med.* **60**:64 (July) 1937. (i) Butt, H. R.; Snell, A. M., and Keys, A.: Plasma Proteins in Hepatic Disease: A Study of the Colloid Osmotic Pressure of Blood Serum and of Ascitic Fluid in Various Diseases of the Liver, *ibid.* **63**:143 (Jan.) 1939. (j) Gray, S. J.: Colloidal Gold Reaction of Blood Serum in Diseases of the Liver, *ibid.* **65**:524 (March) 1940. (k) Ivanov, L. P., and Chervyakovskii, N. Y.: Changes in the Albumin Fraction in the Blood Serum in Liver Disease, abstracted, *Chem. Abstr.* **30**:6808, 1936. (l) O'Hare, J. P., and Driscoll, M.: Blood Proteins in Liver Disease, in *Medical Papers Dedicated to Henry*

(Footnote continued on next page)

ratio may be reversed in the presence of this disease. However, it has not been clear what relation the changes in serum protein bear to the course of the disease and to the formation of ascites.

Snell<sup>2a</sup> has stated that "the ratio tends to return to normal as improvement takes place," although he has not published data pertinent to this observation. Foley, Keeton, Kendrick and Darling<sup>2b</sup> reported data on 1 patient with cirrhosis of the liver and ascites whose ascites disappeared and whose clinical improvement was associated with a return of serum protein values to normal during a period of seven months. Conn, Newburgh, Johnston and Sheldon<sup>3</sup> recorded data on the serum proteins of a patient with hepatic disease, in whom improvement was associated with a rise in serum albumin to normal. This phenomenon occurred over a four month period when the patient had no ascites. O'Hare and Driscoll,<sup>2i</sup> and more recently Gray,<sup>2j</sup> have suggested that there may be a correlation between the extent of alteration of the albumin-globin ratio and the severity of hepatic disease, since patients with more advanced forms of disease of the liver seemed to have more extreme alterations of serum proteins. Tumen and Bockus,<sup>2g</sup> on the contrary, reported as follows:

The ratio of the two proteins to each other fluctuated a great deal during the course of the disease without any striking change in the serum-albumin content, and without there being any apparent variation in the associated liver disturbance.

Likewise, several authors ascribed the formation of ascites in part to changes in the serum proteins. Peters and Eisenman,<sup>2d</sup> Myers and Keefer<sup>2f</sup> and Ivanov and Chervyakovskii<sup>2k</sup> found that the formation of ascites was closely related to a reduction in serum albumin. Butt, Snell and Keys<sup>2i</sup> stated that the colloid osmotic pressure of the serum was reduced in cirrhosis of the liver with ascites and that the lowered pressure was correlated roughly with a reduction in the level of serum albumin. They inferred that a low colloid osmotic pressure may play a part in the formation of ascites. Kellermann<sup>4</sup> found that the colloid osmotic pressure of the serum was reduced in patients with cirrhosis of the liver and ascites. The only comprehensive report of changes in serum protein during formation of ascites or during diuresis and the disappearance of ascites was that made by Foley and associates.<sup>2b</sup>

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Asbury Christian, Baltimore, Waverly Press, Inc., 1936, p. 639. (m) Israel, H. L., and Reinhold, J. G.: Detection of Cirrhosis and Other Diseases of the Liver by Laboratory Tests, *J. Lab. & Clin. Med.* **23**:588, 1937.

3. Conn, J. W.; Newburgh, L. H.; Johnston, M. W., and Sheldon, J. W.: Study of the Deranged Carbohydrate Metabolism in Chronic Infectious Hepatitis, *Arch. Int. Med.* **62**:765 (Nov.) 1938.

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In the present study on patients with cirrhosis of the liver we have attempted to clarify the relationship between serum proteins and hepatic function by following changes in the protein fractions of serum, both during clinical improvement and during hepatic failure. Our results confirm the suggested correlation between the functional competence of the liver and changes in serum proteins. The trend of changes in the serum proteins, particularly in the serum albumin, is of prognostic significance. Furthermore, the formation of ascites seems to depend in part on the level of the serum albumin.

The data contained in this report represent part of the results of a four year study of patients with cirrhosis of the liver.<sup>5</sup> Serum proteins were determined at monthly intervals while the patients were in the hospital and every two months after their discharge.<sup>6</sup>

#### RELATION OF THE SERUM PROTEIN LEVEL TO THE CLINICAL COURSE

In figure 1 is charted the frequency distribution of values for serum albumin and for serum globulin determined for 61 patients at the time of their admission to the hospital. It is apparent that the general distribution falls beyond the normal range, a deviation which confirms reports by other workers.<sup>7</sup> The clinical states of the patients at the times these values were obtained varied considerably. Some patients had jaundice, ascites and edema. Others had only ascites or only jaundice. In still others the presenting problem was hematemesis. Thus the distribution of values is that of a heterogeneous group of patients, all, however, with cirrhosis of the liver.

Tables 1 through 6 record the changes in serum proteins occurring in these 61 patients throughout the period of study. Since the patients were seen in different stages of the disease and since there might well have been a correlation between the level of protein in the blood at the time of entry and the clinical outcome with respect to duration of life, the subjects were classified on the basis of prognosis. No patient was included if the course of his illness was terminated by a fatal episode unrelated to hepatic failure, such as primary carcinoma of the liver, carcinoma of the bile ducts, thrombosis of the portal vein, Pick's polyserositis or death following operation for an incarcerated umbilical hernia.

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5. Patek, A. J., Jr., and Post, J.: Treatment of Cirrhosis of the Liver by a Nutritious Diet and Supplements Rich in Vitamin B Complex, *J. Clin. Investigation* 20:481, 1941.

6. The serum proteins were determined by the Howe method of precipitating the globulin fraction, together with the mico-Kjeldahl distillation technic.

7. Filinski.<sup>1</sup> Footnote 2 *a-b*.

The range of values for serum albumin, determined at the time of admission to the hospital, has been tabulated for a group of patients who improved and for a group of those who died. The 28 patients who made

Range of Values for Serum Albumin, Gm. per 100 Cc.	Number of Patients Who Died	Number of Patients Who Improved
1.5 - 2.5	14	7
2.5 - 3.5	6	15
3.5 - 4.5	0	5
4.5 - 5.0	0	1
Mean value and standard deviation, Gm. per 100 Cc.	$2.4 \pm 0.5$	$3.0 \pm 0.7$

clinical improvement were those included in tables 1 through 4. Improvement was measured by diuresis, with disappearance of ascites,

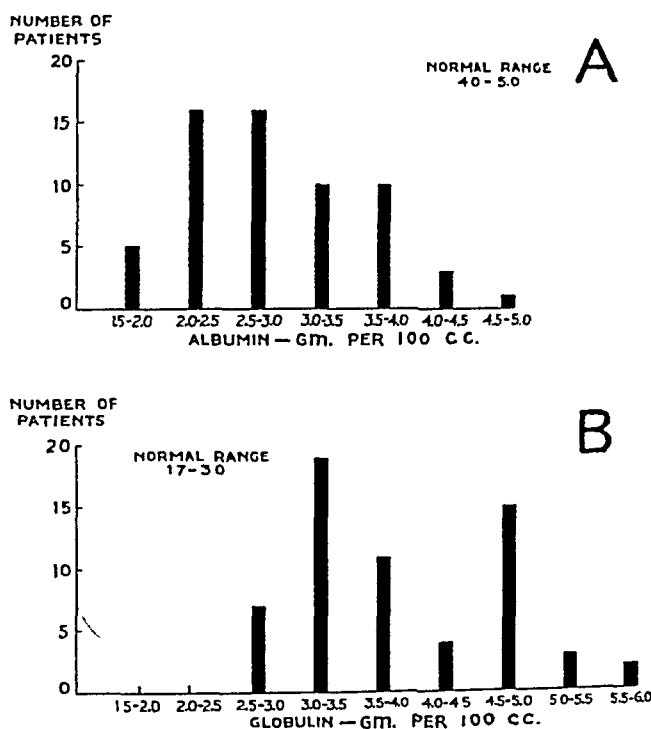


Fig. 1.—Frequency distribution of values for serum protein determined at the time of admission to the hospital for 61 patients with cirrhosis of the liver. *A*, values for serum albumin. *B*, values for serum globulin. In both instances the values fall wide of the normal range.

and by a return to previous strength and well-being. In certain patients (tables 1 and 2) these changes seemed nearly permanent. In others (tables 3 and 4) they were temporary or incomplete. Although some of the latter patients ultimately died of hepatic failure, the period of survival after admission to the hospital was never less than twelve months. In sharp contrast is the outcome of illness in the 20 patients (table 6) who failed to show any sustained improvement and whose course was generally characterized by progressive hepatic failure. The average survival period was three months.

The difference between the mean values for serum albumin for the two groups of patients is statistically significant. Therefore it appears that the level of the serum albumin has a prognostic value. Further examination of these data shows that all patients who died had ascites on admission to the hospital and that only 2 experienced a partial diuresis, which was temporary. These patients (44 and 49, table 6) had values for serum albumin of 2.9 and 3.3 Gm. per hundred cubic centimeters respectively on entry. However, 6 of the 28 patients who improved had no ascites. Their initial values for serum albumin ranged between 3.5 and 5.0 Gm. per hundred cubic centimeters.

When one compares only the values for patients who had ascites, the mean is 2.4 Gm. per hundred cubic centimeters (standard deviation  $= \pm 0.5$  Gm.) for those who died and 2.7 Gm. (standard deviation  $= \pm 0.5$  Gm.) for those who improved. The difference between the means is not statistically significant. Of the 20 patients who died, 70 per cent had serum albumin levels below 2.5 Gm. per hundred cubic centimeters. On the other hand, of the 22 patients who improved, 70 per cent had serum albumin levels above 2.5 Gm. Thus it appears that the prognosis as to duration of life becomes increasingly grave as the level of the serum albumin decreases.

The distribution of the serum globulin values for these same two groups of patients has been tabulated.

Range of Values for Serum Globulin, Gm. per 100 Cc.	Number of Patients Who Died	Number of Patients Who Improved
2.5 - 3.5	8	13
3.5 - 4.5	4	9
4.5 - 5.5	8	6
Mean value and standard deviation, Gm. per 100 Cc.	$3.8 \pm 0.8$	$3.8 \pm 0.7$

There is no difference between the mean values for serum globulin for these two groups. Thus the level of the serum globulin is of no prognostic value.

The range of values for serum total protein of these groups of patients has also been tabulated.

Range of Values for Serum Total Protein, Gm. per 100 Cc.	Number of Patients Who Died	Number of Patients Who Improved
5.0 - 6.0	7	4
6.0 - 7.0	11	11
7.0 - 8.0	2	11
8.0 - 9.0	0	2
Mean, Gm. per 100 Cc.	6.2	6.6

These data show a possibly higher range distribution for those patients who improved. However, since the normal range of values for the serum total protein is between 6.0 and 8.0 Gm. per hundred cubic centimeters, any variation from patient to patient within this range is meaningless.

TABLE 1.—Changes in Values for Serum Proteins in

No.	Period of Observation		Month												
			0	1	2	3	4	5	6	7	8	9	10	11	12
1	3/29/39 to 6/29/39	Albumin	3.3	† 4.1	4.3	...	...	...	...	...	...	...	...	...	...
		Globulin	3.2	3.5	3.4	...	...	...	...	...	...	...	...	...	...
2	4/28/36 to 9/25/36	Albumin	3.3	† 4.1	4.3	4.4	4.3	4.7	...	...	...	...	...	...	...
		Globulin	3.8	4.4	4.3	3.8	3.6	3.7	...	...	...	...	...	...	...
3	7/ 1/39 to 4/ 2/40	Albumin	2.4	† 3.0	3.5	4.2	4.1	3.9	3.9	3.8	4.4	3.9	4.2	...	...
		Globulin	3.5	3.0	3.1	2.8	2.6	2.9	2.8	1.9	2.0	2.7	2.8	...	...
4	8/ 6/37 to 1/16/38	Albumin	1.8	2.5	† 3.4	3.9	4.0	...	3.2	...	...	...	...	...	...
		Globulin	3.5	4.5	4.2	3.6	3.7	...	3.6	...	...	...	...	...	...
5	3/21/39 to 9/11/39	Albumin	3.5	2.1	2.1	2.4	2.8	† 3.0	3.2	...	...	4.0	...	...	...
		Globulin	3.1	3.9	3.9	4.0	3.9	3.8	3.6	...	...	3.5	...	...	...
6	4/ 2/37 to 10/ 6/37	Albumin	2.2	?	2.5	2.9	† 3.0	3.2	3.3	3.5	...	...	3.4	...	...
		Globulin	3.5	3.3	2.9	† 3.5	3.4	3.3	3.2	...	...	...	3.7	...	...
7	1/28/38 to 6/ 5/39	Albumin	2.7	3.1	† 3.6	3.8	...	3.8	...	...	3.4	3.4	...	3.5	3.7
		Globulin	4.7	4.1	4.5	3.0	...	3.5	...	...	3.1	3.3	...	3.3	2.8
8	12/20/37 to 5/ 4/39	Albumin	† 3.0	4.1	4.8	3.9	4.6	4.6	5.4	...	5.0	4.6	4.8	4.9	4.8
		Globulin	3.6	4.2	3.7	2.3	2.8	2.7	2.4	...	2.9	2.5	2.4	2.7	2.1
9	5/ 9/38 to 3/ 1/40	Albumin	3.2	2.8	3.2	3.1	3.3	2.8	† 3.1	3.3	3.5	3.4	3.7	3.4	4.1
		Globulin	2.9	3.1	3.2	3.2	3.7	4.3	4.5	4.4	4.2	4.3	4.2	3.8	4.3
10	1/ 7/38 to 11/25/39	Albumin	3.3	3.4	3.1	3.5	2.9	3.0	2.9	...	† 3.3	3.6	3.9	3.9	4.1
		Globulin	3.5	3.7	3.5	2.3	2.1	2.2	2.1	...	2.5	2.8	2.6	2.8	2.7
11	10/ 5/36 to 1/18/38	Albumin	2.2	2.6	† 3.4	3.4	3.6	3.5	3.7	3.9	...	3.9	...	4.3	4.4
		Globulin	2.8	2.6	2.9	3.3	3.2	3.0	3.0	3.4	...	3.1	...	3.1	3.8
12	9/22/36 to 6/ 1/40	Albumin	2.3	...	3.3	† 3.8	4.1	4.1	4.3	3.9	4.5	4.5	...	4.0	4.2
		Globulin	3.6	...	2.3	4.0	4.0	3.3	3.5	3.5	3.9	3.9	...	3.9	3.1
			Weeks												
			0	1	2	6	8	8½	10	14	18	22	30	34	38
13	1/14/38 to 5/ 8/39	Albumin	2.8	3.1	† 3.1	3.0	2.5	2.5	2.1	† 3.2	3.4	3.5	3.7	3.7	3.8
		Globulin	4.5	4.9	4.5	4.7	4.5	4.2	3.2	4.2	3.9	3.3	3.4	3.2	3.0

\* Heavy type indicates the presence of ascites, and light type indicates the absence of ascites.

† Approximate time of onset of diuresis.

TABLE 2.—Changes in Values for Serum Proteins in

No.	Period of Observation		Month												
			0	1	2	3	4	5	6	7	8	9	10	11	12
14	1/26/37 to 10/ 9/37	Albumin	3.7	3.8	4.2	4.2	3.7	3.9	3.9	4.2	3.9	...	...	...	...
		Globulin	3.9	3.6	3.0	2.9	3.3	3.0	3.1	3.1	2.7	...	...	...	...
15	11/27/36 to 4/ 1/37	Albumin	4.2	4.2	4.2	4.3	4.4	...	...	...	...	...	...	...	...
		Globulin	4.5	3.8	3.8	3.5	3.2	...	...	...	...	...	...	...	...
17	11/ 1/38 to 3/16/40	Albumin	3.6	4.0	4.5	4.8	4.6	4.9	4.6	4.9	4.5	4.6	...	4.7	4.4
		Globulin	3.6	3.1	3.5	3.4	3.4	2.7	3.1	3.1	3.3	3.3	...	2.9	3.6
18	10/19/39 to 4/25/40	Albumin	4.3	3.7	...	...	...	...	...	4.5	4.4	4.0	5.2	5.1	...
		Globulin	3.3	3.2	...	...	...	...	...	3.3	3.1	2.9	2.7	2.7	...
16	3/13/37 to 12/23/37	Albumin	3.7	3.3	3.9	...	4.1	3.8	4.1	3.9	...	3.9	4.9	...	...
		Globulin	3.1	2.0	2.4	...	3.0	2.8	3.0	3.0	...	2.5	2.8	...	...
19	12/28/37 to 2/11/39	Albumin	3.9	4.1	4.3	4.4	4.2	4.6	...	...	4.3	4.0	4.4	4.6	4.5
		Globulin	4.7	4.6	4.3	3.0	2.8	3.0	...	...	3.6	3.4	3.2	2.7	2.6
20	4/28/37 to 9/ 1/39	Albumin	3.8	4.5	4.3	4.4	4.6	4.4	...	4.8	...	4.8	...	5.0	4.9
		Globulin	2.7	2.9	2.3	2.9	2.7	2.8	...	2.5	...	2.5	...	3.3	3.4

*Patients with Ascites Who Made Clinical Improvement \**

Month												Comment
13	14	15	16	18	20	22	26	30	36	40	45	
...	...	...	...	...	...	...	...	...	...	...	...	Gastrointestinal hemorrhage in seventh month of observation
...	...	...	...	...	...	...	...	...	...	...	...	Massive fatal gastrointestinal hemorrhage in sixth month of observation; diagnosis at necropsy: cirrhosis of liver and ruptured esophageal varix
...	...	...	...	...	...	...	...	...	...	...	...	Evidence of recent gastrointestinal hemorrhage when observation was begun; dehydration
...	...	...	...	...	...	...	...	...	...	...	...	Admission to hospital 2/13/38; death 2/15/38; diagnosis at necropsy: uremia, chronic pyelonephritis, arteriosclerosis and cirrhosis of liver
3.8	3.9	4.0	3.8	3.8	...	4.3	4.4					
3.0	3.0	3.1	3.0	3.2	...	3.5	2.8					
4.3	4.9	5.0	...	...	...	...	...	...	...	...	...	Death 5/4/39; diagnosis at necropsy: cerebrovascular syphilis with thrombosis, bronchopneumonia and cirrhosis of liver
2.3	2.9	2.3										
4.3	4.2	4.0	4.0	3.8	...	4.5						
4.0	3.9	3.9	3.7	3.8	...	3.5						
3.5	4.1	3.8	...	3.9	4.6	...	...	4.7	...	...	...	Operation for strangulated umbilical hernia in thirteenth month of observation
2.6	3.0	3.1	...	3.1	3.3	...	...	2.7				
...	4.4	4.3	4.0	4.4	...	4.1	4.4	4.4	4.5	4.9		
...	4.2	3.2	2.8	3.3	...	2.9	2.9	3.1	2.6	3.1		
...	4.5	4.7	4.7	...	5.3	...	4.3	4.7	4.4	4.5	4.5	
...	2.7	2.6	2.6	...	2.8	...	3.3	3.2	3.0	2.5	2.7	
Weeks												
42	46	50	54	60	62	69	75	85				
3.9	3.8	3.7	3.9	3.8	3.8	3.9	4.3	4.5				Acute glomerulonephritis in eighth week of observation; infection of the upper respiratory tract with jaundice and edema lasting 1 week during sixtieth week of observation
3.3	3.0	2.7	3.4	3.3	† 3.6	3.2	3.2	3.3				

The question mark indicates that the presence of ascites was not excluded.

*Patients Without Ascites Who Made Clinical Improvement*

Month											Comment
13	14	15	16	18	19	22	25	28	31	32	
...	...	...	...	...	...	...	...	...	...	...	Severe jaundice; malnutrition
...	...	...	...	...	...	...	...	...	...	...	Malnutrition; peripheral neuritis
...	...	...	...	...	...	...	...	...	...	...	Jaundice; peripheral neuritis
...	...	...	...	...	...	...	...	...	...	...	Peripheral neuritis
...	4.8	...	...	...	...	...	...	4.9	...	...	Severe jaundice; peripheral neuritis
...	3.5	...	...	...	...	...	...	2.8			
...	...	...	5.0	5.2	5.3	...	...	...	...	...	Malnutrition; peripheral neuritis
...	...	...	3.4	3.4	2.4						
4.6	5.3	5.6	...	5.1	4.9	...	4.9	5.6	4.9	5.5	Malnutrition; peripheral neuritis
2.7	2.0	1.9	...	2.5	2.3	...	2.7	2.2	3.1	2.4	



Apparently the levels of total protein and of globulin in the serum are without prognostic import in cases of cirrhosis of the liver. However, there is some correlation between the level of serum albumin and the prognosis as to duration of life.

The progressive changes in serum proteins during the course of cirrhosis of the liver were then examined. In table 1 are listed data for 13 patients who had ascites on admission and who subsequently

TABLE 3.—Changes in Values for Serum Proteins for

No.	Period of Observation		Month												
			0	1	2	3	4	5	6	7	8	9	10	11	12
22	7/7/38 to 3/10/40	Albumin	2.9	3.4	3.6	3.5	3.8	3.5	2.9	3.3	3.7	...	...	...	2.8
		Globulin	3.2†	3.4 †	3.2	2.7	3.0	2.8	2.5‡	4.1 †	3.4	...	...	...	2.8‡

\* Heavy type indicates the presence of ascites, and light type indicates the absence of ascites.

† Approximate time of onset of diuresis.

‡ Gastrointestinal hemorrhage.

TABLE 4.—Changes in the Values for Serum Proteins for

No.	Period of Observation		Month												
			0	1	2	3	4	5	6	7	8	9	10	11	12
23	1/ 7/38 to 8/16/39	Albumin	2.4	2.6 †	2.6	2.5	2.8	2.5	2.4	...	2.8	2.7	2.9	3.0	2.9
		Globulin	4.8	5.2	4.3	3.0	3.4	3.4	3.5	...	3.3	3.1	3.3	3.5	3.1
24	12/29/37 to 4/25/40	Albumin	3.2	2.9	3.3	3.1 †	3.1	3.5	3.4	...	...	3.7	3.3	3.1	3.1
		Globulin	3.3	3.9	3.3	3.3	3.5	3.5	3.3	...	...	3.6	3.4	3.5	3.5
27	11/ 5/38 to 3/18/39	Albumin	2.9	3.1 †	3.0	3.1	3.4	...	...	3.7	...	...	...	...	...
		Globulin	4.5	4.8	4.2	4.4	4.1	...	...	4.6	...	...	...	...	...
28	5/24/39 to 5/24/40	Albumin	2.9	2.6	2.7 †	2.9	3.4	3.4	3.3	3.3	2.8	3.5	3.6	3.4	3.2
		Globulin	5.7	4.9	4.6	4.0	4.1	3.9	5.1	4.9	4.8	4.0	3.9	4.0	3.9
29	1/12/39 to 11/ 1/40	Albumin	2.7	2.4 †	2.7	3.5	3.1	2.7	2.7	3.2	3.0	3.1	3.4	3.3	3.2
		Globulin	3.3	3.1	3.5	3.0	3.4	2.9	2.6	2.7	3.0	3.1	3.1	3.1	3.1
25	12/20/37 to 3/ 5/40	Albumin	2.5 †	3.0	3.1	3.3	3.3	3.4	3.3	3.1	...	3.0	3.0	3.2	2.9
		Globulin	3.4	5.1	5.1	5.1	4.1	3.9	3.8	3.5	...	4.4	4.4	4.3	4.2
26	9/16/37 to 1/23/40	Albumin	1.8	2.0	2.2	2.1	1.9	2.0	2.3	2.2	2.2	2.6	2.4	...	2.7
		Globulin	5.3	5.0	4.7	4.4	5.3	5.6	5.7	5.1	4.4	4.6	3.6	...	5.0

\* Heavy type indicates the presence of ascites, and light type indicates the absence of ascites.

† Approximate time of onset of diuresis.

? Question mark indicates that the presence of ascites was not excluded.

improved. All of them showed the classic signs of decompensated cirrhosis of the liver. On admission their values for serum albumin ranged from 1.8 to 3.5 Gm. per hundred cubic centimeters. It is apparent that a sustained rise in the amount of serum albumin attended clinical improvement and diuresis. In all patients but 1 (patient 6) the serum albumin rose to normal. In some instances the value for serum globulin returned to normal, whereas in others it remained somewhat elevated. It is of further interest that the changes in serum proteins in these patients generally occurred over many weeks.

The albumin and globulin values for 7 patients who were less severely ill are recorded in table 2. None of the patients had ascites; nevertheless, all of them revealed ample evidence of cirrhosis of the liver. Patients 14 and 16 were extremely jaundiced. All but patient 14 showed severe peripheral neuritis. Although the deviations from normal were less pronounced than those recorded in table 1, there was a definite tendency toward reduced values for albumin and increased values for

*Patient 22, Who Had Repeated Gastrointestinal Hemorrhages\**

Month							Comment
13	14	15	16	17	18	19	
3.1	3.2	3.6	...	3.6	3.9	3.7	Death 3/10/40; diagnosis at necropsy: cirrhosis of liver, ruptured esophageal varix and thrombosis of portal vein
3.1	† 3.0	3.2	...	3.1	3.2	3.3†	

*Patients with Ascites Who Made Partial Clinical Improvement\**

Month																Comment
13	14	15	16	18	19	20	21	22	23	24	25	26	27	28	29	
3.1	3.2	3.3	2.9	2.9	2.8	3.4	...	...	...	...	...	...	...	...	...	Death November 1939; no necropsy
3.1	3.3	3.2	2.8	2.9	3.2	3.5	...	...	...	...	...	...	...	...	...	
3.3?	3.2?	3.5?	3.6?	3.4	3.7	3.6	3.1	3.1	3.2	3.4	3.5	3.5	2.8	...	...	Suspected thrombosis of splenic and portal veins; death 4/25/40; no necropsy
3.0	3.3	3.6	3.4	3.2	3.0	3.4	3.7	3.4	3.4	3.5	3.3	3.1	3.5			
...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	Patient last observed in June 1939; no ascites; general health poor
...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	Patient still under observation
3.3	3.5	3.1	3.1	3.0	3.0	...	2.7	...	...	...	...	...	...	...	...	Patient still under observation
2.9	2.9	2.8	2.8	3.0	2.8	...	2.9									
3.1	3.3	3.1	3.3	3.5	3.5	3.5	3.3	3.3	...	3.2	3.1	2.4	...	...	...	Death 3/5/40; diagnosis at necropsy: cirrhosis of liver
3.8	3.5	3.1	3.0	3.4	3.4	3.9	3.9	4.0	...	3.5	3.6	3.4				
2.9†	3.0	2.7	2.8	2.8	2.7	3.0	3.2	3.0	...	2.9	...	2.9	2.6	2.8	2.2	Death 1/23/40; diagnosis at necropsy: carcinoma of liver with primary metastasis to portal vein, lungs and adrenals and cirrhosis of liver
4.6	4.8	4.8	5.0	4.5	5.2	4.8	4.8	4.5	...	4.5	...	4.7	5.2	4.8	4.0	

globulin at the time of admission. The initial value for albumin ranged from 3.6 to 4.3 Gm. per hundred cubic centimeters. Improvement in the general clinical state was accompanied by a change toward normal values both for albumin and for globulin.

In contrast to the foregoing data are those for the 7 patients included in table 4. The clinical condition of the latter patients appeared to be similar to that of the patients listed in table 1, both during the state of decompensation and during temporary improvement. The level of serum albumin on entry ranged from 1.8 to 3.2 Gm. per hundred cubic

TABLE 5.—Changes in Values for Serum Proteins in Patients Whose Hepatic Disease Was Complicated or Who Were Incompletely Studied\*

No.	Period of Observation		Month															Comment	
			0	1	2	3	4	5	6	7	8	9	10	11	12	13	14		15
30	10/14/38 to 11/10/38	Albumin Globulin	3.7 2.6	3.8 2.6	...	...	...	...	...	...	...	...	...	...	...	...	...	...	Death 11/26/38; diagnosis at necropsy: primary carcinoma of liver, cirrhosis of liver and generalized arteriosclerosis
31	2/23/38 to 4/21/38	Albumin Globulin	2.6 5.8	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	Death 4/21/38, after operation for strangulated, incarcerated umbilical hernia; cirrhosis of liver diagnosed after biopsy
32	2/25/38 to 3/ 6/38	Albumin Globulin	2.3 5.0	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	Patient signed out at own request
33	11/20/38 to 1/ 7/37	Albumin Globulin	2.7 3.4	2.9 3.7	...	...	...	...	...	...	...	...	...	...	...	...	...	...	Death 1/7/37; diagnosis at necropsy: primary carcinoma of liver, cirrhosis of liver and intraperitoneal hemorrhage
34	1/ 6/38 to 1/15/38	Albumin Globulin	2.5 4.5	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	Patient discharged 1/15/38 to Psychiatric Division of Bellevue Hospital; death January 1938; no necropsy; diabetes mellitus
35	8/18/37 to 8/20/37	Albumin Globulin	2.2 3.1	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	Death 8/20/37; diagnosis at necropsy: primary carcinoma of liver and cirrhosis of liver
36	8/18/37 to 9/24/37	Albumin Globulin	3.5 4.4	3.3 4.4	...	...	...	...	...	...	...	...	...	...	...	...	...	...	Patient signed out at own request
37	3/23/38 to 1/16/39	Albumin Globulin	3.6 4.3	3.4 3.2	3.1 3.5	3.2 3.1	...	3.4 2.8	2.8 3.2	3.1 3.3	3.5 2.7	3.6 3.3	...	...	...	...	...	...	Death 1/16/39; diagnosis at necropsy: cirrhosis of liver, thrombosis of portal vein and infarcts of liver due to thromboses
38	10/22/37 to 12/20/38	Albumin Globulin	2.9 3.4	2.8 3.3	2.7 3.9	2.7 5.9	3.5 6.1	2.9 5.0	2.7 4.3	2.9 3.2	2.7 3.1	2.8 3.1	...	3.0 3.6	2.7 3.6	2.7 3.3	2.0 2.3	...	Death 12/20/38; diagnosis at necropsy: cirrhosis of liver, Pick's polyserositis and intraperitoneal hemorrhage
39	2/25/38 to 11/ 7/38	Albumin Globulin	2.7 2.9	...	...	...	...	...	3.2 3.0	...	...	3.1 3.2	...	...	...	...	...	...	Observed at irregular intervals
40	5/22/39 to 2/17/40	Albumin Globulin	2.4 4.7	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	Patient followed incompletely; discharged 2/17/40 to Psychiatric Division of Bellevue Hospital; diagnosis: cerebral arteriosclerosis
41	11/ 6/37 to 4/ 3/38	Albumin Globulin	4.4 1.9	4.1 2.2	3.6 3.0	3.9 3.3	3.2 3.3	...	...	...	...	...	...	...	...	...	...	...	Death 4/3/38; diagnosis at necropsy: primary carcinoma of bile ducts with metastasis to porta hepatis, biliary cirrhosis of liver and recanalization of thrombosed intrahepatic portal veins
21	8/14/39 to 11/22/39	Albumin Globulin	4.4 2.5	...	...	...	4.5 2.6	...	...	...	...	...	...	...	...	...	...	...	Cirrhosis of liver diagnosed after biopsy; patient observed at irregular intervals

\* Heavy type indicates the presence of ascites, and light type indicates the absence of ascites.

† Approximate time of onset of diuresis.

TABLE 6.—Changes in Values for Serum Proteins in Patients Who Died of Cirrhosis of the Liver\*

No.	Period of Observation		Month												Comment
			0	1	2	3	4	5	6	7	8	9	10	11	
43	9/16/37 to 10/11/37	Albumin Globulin	2.4 2.7	...	...	...	...	...	...	...	...	...	...	...	Death 10/11/37; diagnosis at necropsy: cirrhosis of liver, pneumococci pericarditis and bronchopneumonia
58	1/ 3/39 to 1/24/39	Albumin Globulin	2.7 4.1	...	...	...	...	...	...	...	...	...	...	...	Death 1/24/39; diagnosis at necropsy: cirrhosis of liver and ruptured esophageal varix
59	12/ 5/39 to 1/ 5/40	Albumin Globulin	2.8 3.9	...	...	...	...	...	...	...	...	...	...	...	Death 1/5/40; no necropsy
61	7/ 7/38 to 8/ 9/38	Albumin Globulin	1.9 4.9	2.0 4.4	...	...	...	...	...	...	...	...	...	...	Death 8/9/38; diagnosis at necropsy: cirrhosis of liver
42	9/22/36 to 10/18/36	Albumin Globulin	2.3 2.6	1.7 3.5	...	...	...	...	...	...	...	...	...	...	Death 10/18/36; diagnosis at necropsy: cirrhosis of liver
45	9/17/38 to 10/18/38	Albumin Globulin	2.3 3.2	2.3 2.9	...	...	...	...	...	...	...	...	...	...	Death 10/18/38; diagnosis at necropsy: cirrhosis of liver and acute diffuse peritonitis
46	7/12/38 to 9/13/38	Albumin Globulin	2.1 4.6	2.4 3.8	...	...	...	...	...	...	...	...	...	...	Death 9/13/38; no necropsy
47	10/14/37 to 11/19/37	Albumin Globulin	2.2 4.5	1.9 4.8	...	...	...	...	...	...	...	...	...	...	Death 11/19/37; diagnosis at necropsy: cirrhosis of liver
48	11/ 3/37 to 12/11/37	Albumin Globulin	2.0 3.1	2.0 3.8	...	...	...	...	...	...	...	...	...	...	Death at home, February 1938; no necropsy
51	6/ 4/37 to 6/29/37	Albumin Globulin	1.5 4.7	1.4 4.8	...	...	...	...	...	...	...	...	...	...	Death 6/29/37; diagnosis at necropsy: cirrhosis of liver
53	8/25/37 to 9/21/37	Albumin Globulin	1.8 3.9	1.8 3.4	...	...	...	...	...	...	...	...	...	...	Death 9/21/37; no necropsy
56	7/18/39 to 9/12/39	Albumin Globulin	1.9 3.8	1.8 3.8	...	...	...	...	...	...	...	...	...	...	Death 9/12/39; no necropsy
57	1/20/37 to 2/16/37	Albumin Globulin	3.0 4.5	2.8 5.3	...	...	...	...	...	...	...	...	...	...	Death 2/15/37; diagnosis at necropsy: cirrhosis of liver
60	4/ 3/40 to 5/23/40	Albumin Globulin	2.1 4.5	...	...	...	...	...	...	...	...	...	...	...	Death 5/23/40; no necropsy
50	9/28/37 to 12/ 2/37	Albumin Globulin	2.3 4.8	1.8 4.5	1.8 5.2	...	...	...	...	...	...	...	...	...	Death 12/2/37; diagnosis at necropsy: cirrhosis of liver, thrombosis of portal vein and duodenal ulcer
52	4/ 3/37 to 6/14/37	Albumin Globulin	2.2 3.2	2.4 2.9	2.9 3.3	...	...	...	...	...	...	...	...	...	Death 6/14/37; diagnosis at necropsy: cirrhosis of liver
55	8/28/39 to 1/ 9/40	Albumin Globulin	2.1 4.5	2.2 5.2	2.2 4.9	2.0 4.7	2.0 4.8	...	...	...	...	...	...	...	Death 1/9/40; diagnosis at necropsy: cirrhosis of liver
44	12/ 8/37 to 3/24/38	Albumin Globulin	2.9 2.7	+ 3.7 4.0	3.3 3.4	3.3 2.1	...	...	...	...	...	...	...	...	Death 3/24/38; diagnosis at necropsy: cirrhosis of liver and ruptured esophageal varix
54	2/10/39 to 8/ 5/39	Albumin Globulin	3.0 3.3	2.7 3.2	2.8 2.7	3.3 2.1	2.8 2.5	2.8 2.6	2.7 2.2	2.8 1.8	2.3 1.9	...	...	...	Death 8/5/39; diagnosis at necropsy: cirrhosis of liver and duodenal ulcer
49	10/28/37 to 9/30/38	Albumin Globulin	3.3 2.8	+ 3.4 3.0	3.4 3.0	3.7 4.3	3.4 4.3	3.1 3.5	3.4 3.4	3.3 3.2	3.0 3.7	...	2.6 4.0	2.7 3.9	Death at home, December 1938; no necropsy; intraperitoneal hemorrhage (?)

\* Heavy type indicates the presence of ascites, and light type indicates the absence of ascites.

+ Approximate time of onset of diuresis.

centimeters. Each of the 7 patients experienced at least one period of diuresis and a concomitant rise in the level of the serum albumin. However, in no case did the level of serum albumin remain normal over long periods of observation, in spite of clinical well-being during part of the time.

The course of patient 25 (table 4) is worthy of mention. This 54 year old man was admitted with massive ascites, edema and jaundice. The albumin-globulin ratio was 2.5:3.4. During the first six weeks of his stay in the hospital complete diuresis occurred and the jaundice disappeared. After this improvement he gained 20 pounds (9.1 Kg.). He was free of ascites and in good general health for two years. However, the level of serum albumin never became normal; it varied between 3.1 and 3.5 Gm. per hundred cubic centimeters, while values for serum globulin ranged between 2.9 and 5.1 Gm. Because of the persistently abnormal blood protein pattern the patient was considered to have poor "liver reserve." In spite of this, he left the hospital apparently in good health, only to return in three weeks with massive edema and ascites. The level of serum albumin had fallen to 2.4 Gm. per hundred cubic centimeters and that of serum globulin to 3.4 Gm. He died after three days. At autopsy the diagnosis of cirrhosis of the liver was confirmed.

Patients 23 and 24 (table 4) died, but no autopsy was performed in either instance. The condition of patient 26 was complicated by the presence of a primary carcinoma of the liver. We have been unable to follow patient 27. When last seen she had jaundice, but no ascites, and appeared to be in poor health. Patient 29 left the hospital in June 1940 in good condition. His serum albumin did not change significantly during the succeeding months, until September 7, when it was 2.6 Gm. per hundred cubic centimeters. On September 21 he was seen again, and at this time he was in poor general condition, with massive ascites and moderate edema of the legs. The value for serum albumin was 2.7 Gm. per hundred cubic centimeters and that for globulin 2.9 Gm. Patient 28 is still under observation. This patient has had complete diuresis, with marked clinical improvement. However, over a period of eight months the level of serum albumin has failed to become normal, and for this reason the patient is included in this group.

The course of these 7 patients is in sharp contrast to that of the patients whose values for blood protein are recorded in tables 1 and 2. Some of the latter have been followed for as long as three and one-half years after discharge from the hospital. During this time they have remained in good health. Thus, when clinical improvement is not associated with a sustained rise of serum albumin to normal, or nearly normal, the prognosis as to duration of life must be guarded.

In table 6 are recorded data on 20 patients whose clinical course was characterized by progressive hepatic failure. The course of illness was usually short, averaging three months. In no instance was a sustained rise in serum albumin noted.

#### RELATION OF THE SERUM PROTEIN LEVEL TO THE FORMATION OF ASCITES

Since Starling's<sup>8</sup> original work on the role of the serum proteins in the maintenance of the osmotic pressure of the blood, numerous investigators have stressed the important relation between alterations in the blood proteins and the formation of edema. According to Loeb

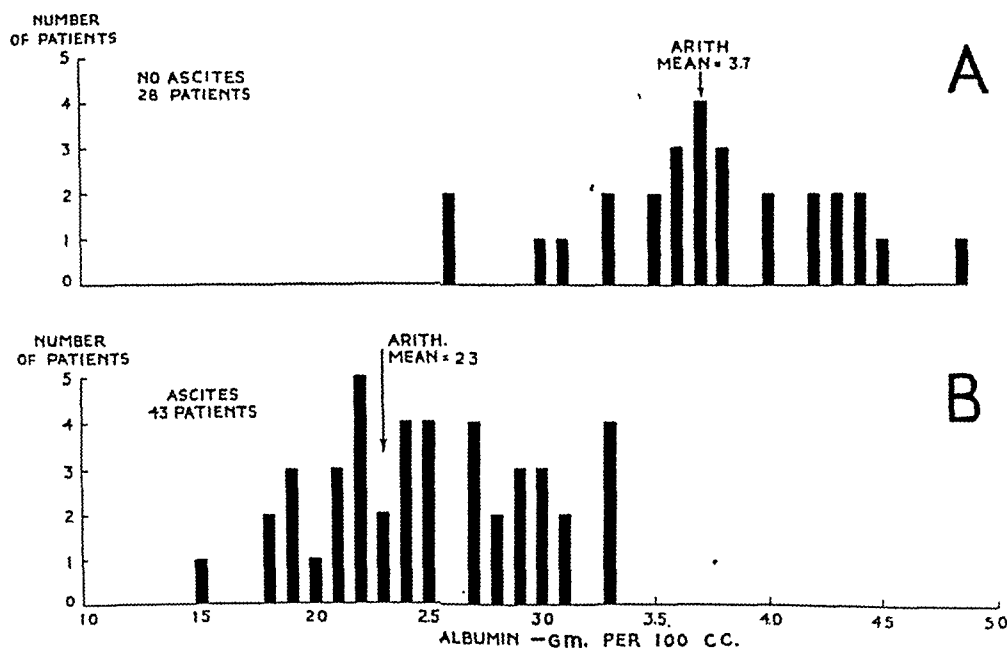


Fig. 2.—Frequency distribution of values for serum protein for patients with and without ascites. *A*, values for serum albumin for 28 patients with cirrhosis of the liver but no ascites. *B*, values for serum albumin for 43 patients with cirrhosis of the liver and ascites. The respective arithmetic mean values are indicated above each graph. Although there is some overlapping in each group, the means are significantly different from each other.

and associates,<sup>9</sup> ascitic fluid may also be considered a transudate. Consequently, a comparison was made of the values for serum proteins for patients with and without ascites. Figure 2 shows the frequency distribution of the values for serum albumin for 43 patients with ascites and 28 patients without ascites. The values recorded for the 43 patients with

8. Starling, E. H.: On the Absorption of Fluids from the Connective Tissue Spaces, *J. Physiol.* **19**:312, 1895.

9. Loeb, R. F.; Atchley, D. W., and Palmer, W. W.: On the Equilibrium Condition Between Blood Serum and Serous Cavity Fluids, *J. Gen. Physiol.* **4**: 591, 1922.

ascites represent those obtained at the time of admission to the hospital. Fifteen patients subsequently experienced complete diuresis and were included, with 13 others, among those without ascites. The values for albumin used for these 15 patients were those determined two months after diuresis was considered complete, in order to be certain of the absence of ascites.

The distribution of values for serum albumin is strikingly different in these two groups. The values for serum albumin for patients with ascites range between 1.5 and 3.3 Gm. per hundred cubic centimeters, whereas those for patients without ascites range between 2.6 and 4.8 Gm. The mean value for the group with ascites is 2.3 Gm. (standard deviation =  $\pm 0.1$ ), whereas that of the group without ascites is 3.7 Gm. (standard deviation =  $\pm 0.8$ ). The means are significantly different. The 2 patients whose level of serum albumin was 2.6 Gm. per hundred cubic centimeters in the absence of ascites had serum globulin values of 5.8 and 4.3 Gm. per hundred cubic centimeters, respectively. It is possible that in these 2 instances the globulin fractions played a significant role as osmotically active colloids. However, we have seen patients with ascites who had albumin and globulin values identical with these. The role of the serum globulin is obscure in this respect. When the mean values for total protein were examined, they were found to be 6.3 Gm. per hundred cubic centimeters for patients with ascites and 7.3 Gm. for those without ascites. For patients with ascites the mean value for serum globulin was 3.9 Gm. per hundred cubic centimeters, and for those without ascites it was 3.7 Gm. These mean values for total protein and for globulin are not significantly different in the two groups of patients.

Our data concerning the occurrence of low levels of serum albumin in patients with cirrhosis of the liver and ascites are similar to those already presented by other authors.<sup>10</sup> We have examined the data of Tumen and Bockus.<sup>28</sup> Of 13 patients with cirrhosis of the liver and ascites, only 1 had a level of serum albumin above 3.5 Gm. per hundred cubic centimeters. Analysis of similar data reported by Foley and co-workers<sup>2b</sup> shows that in 21 cases of cirrhosis of the liver with associated ascites values for serum albumin range between 1.3 and 3.1 Gm. per hundred cubic centimeters. The range of values for serum globulin was 2.3 to 5.7 Gm. Abrami and Wallich<sup>2b</sup> recorded data for 15 patients with cirrhosis of the liver and associated ascites; the values for serum albumin ranged from 1.4 to 3.1 Gm. per hundred cubic centimeters and those for serum globulin from 2.8 to 5.3 Gm. In 2 instances of alcoholism with hepatomegaly, but without ascites, the values for the serum albumin and the serum globulin were each 4 Gm. per hundred cubic

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10. Footnote 2 *b, d, g, h, i* and *l*.

centimeters. Thus it appears that ascites rarely occurs when the level of serum albumin is greater than 3.5 Gm. per hundred cubic centimeters. As suggested by other workers,<sup>11</sup> such a reduction in the serum albumin would lead to decreased osmotic pressure in the blood, which, in turn, would favor the accumulation of ascitic fluid.

It is not implied that reduction of the serum albumin is the only cause for the formation of ascites. It is likely that hypertension of the portal vein plays a contributory part. By direct measurement Thompson, Caughey, Whipple and Rousselot<sup>12</sup> showed that hypertension of the splenic vein occurs in patients with Banti's syndrome. In cases of Laennec's cirrhosis, also, there is ample clinical evidence of increased pressure in the portal system. MacIndoe's<sup>13</sup> perfusion studies, performed on human subjects post mortem, showed increased resistance in the cirrhotic liver when liquid material was perfused through the portal vein.

It seems unlikely that anatomic changes in the liver sufficient to alter the degree of portal pressure could take place within a few days or weeks and could thus promote diuresis, with the loss of ascites. Moreover, the degree of fibrosis in the liver (and presumably of portal hypertension) must vary considerably from patient to patient. If portal hypertension were the sole cause of ascites, there would be no such correlation between the presence of ascites and the level of the serum albumin as was observed. Data for patient 22 indicate that despite clinical and anatomic evidence of severe portal hypertension ascites occurred only after hemorrhage, associated with a loss of blood protein, as well as a loss of blood cells. Diuresis occurred when the level of serum albumin rose.

For these reasons, admittedly speculative, the level of the serum albumin appears to be an essential factor in the formation of ascites. It also seems likely that portal hypertension determines the site at which the transfer of fluid takes place.

#### RELATION OF THE SERUM PROTEIN LEVEL TO DIURESIS

Nineteen instances of diuresis in 17 patients are recorded in tables 1, 3 and 4, as follows: table 1, patients 1 through 11 and patient 13; table 3, patient 22, and table 4, patients 23, 25, 27 and 28. In each instance the diuresis was proved by a decrease in abdominal fluid and

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11. Butt, Snell and Keys.<sup>21</sup> Ivanov and Chervyakovskii.<sup>2k</sup> Kellermann.<sup>4</sup>

12. Thompson, W. P.; Caughey, J. L.; Whipple, A. O., and Rousselot, L. M.: Splenic Vein Pressure in Congestive Splenomegaly (Banti's Syndrome), *J. Clin. Investigation* **16**:571, 1937.

13. MacIndoe, A. H.: Vascular Lesions of Portal Cirrhosis, *Arch. Path.* **5**: 23 (Jan.) 1928.



by a negative water balance. It is difficult to fix the exact time at which the onset of diuresis occurs, because this phenomenon may persist for several weeks. On this account the temporal relationship of diuresis and the level of serum albumin can only be approximated. The mean value for serum albumin at the onset of diuresis was 3.1 Gm. per hundred cubic centimeters (standard deviation =  $\pm 0.2$  Gm.) and the mean value for serum globulin was 4.1 Gm. (standard deviation =  $\pm 0.7$  Gm.). The level of albumin is near the transition point between that of the group of patients with ascites and that of the group without ascites, as illustrated in figure 2.

It is seen that, particularly in those patients (except patient 6) who improved and who had complete loss of ascites, the level of serum albumin steadily rose to normal. The rise in serum albumin accompanying diuresis does not necessarily indicate a causal relationship, since both might reflect improved hepatic function. However, the rise in serum albumin, which would produce a higher osmotic pressure in the blood, would of itself tend to promote diuresis.

#### SUMMARY AND CONCLUSIONS

Of 61 patients with cirrhosis of the liver, 54 had an abnormal albumin-globulin ratio on admission to the hospital. These data confirm the reports of other authors.

The prognosis as to duration of life becomes increasingly grave as the level of serum albumin decreases. The levels of the serum globulin and the serum total protein have no such prognostic significance.

There is a direct correlation between the level of the serum albumin and the clinical course. Clinical improvement is associated with a rise in serum albumin toward normal. In instances of clinical failure there is no sustained rise.

The level of serum albumin is significantly lower in patients with ascites than in those without ascites.

Diuresis is associated with a rise in serum albumin. The mean value for serum albumin at which diuresis occurs is 3.1 Gm. per hundred cubic centimeters (standard deviation =  $\pm 0.2$  Gm.).

From the data presented, it appears that a reduction in serum albumin is an essential factor in the formation of ascites.

Mr. Walter Meyer gave technical assistance.

# SERUM PROTEINS IN CIRRHOSIS OF THE LIVER

## II. NITROGEN BALANCE STUDIES ON FIVE PATIENTS

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It has not been clear from clinical studies whether the low values for serum albumin associated with cirrhosis of the liver are due to altered protein synthesis or to protein starvation, caused either by low protein intake or by faulty assimilation. Peters and Eisenman<sup>1</sup> ascribed such hypoalbuminemia to insufficient protein intake. Myers and Keefer,<sup>2</sup> however, observed 2 patients with cirrhosis of the liver and ascites and suggested that the hypoproteinemia was due to altered blood protein synthesis associated with the diminished hepatic function. The low serum albumin levels of their patients were unchanged during long periods of high protein feeding, although normal fecal nitrogen values during these periods indicated that the protein was assimilated. Grabfield and Prescott<sup>3</sup> reported a positive nitrogen balance for 1 patient who had cirrhosis of the liver without ascites, but with normal blood proteins.

According to Ling<sup>4</sup> and Liu, Chu, Wang and Chung,<sup>5</sup> when patients with starvation hypoproteinemia are fed 1 to 2 Gm. of protein per kilogram of body weight they respond with a significant rise in serum albumin within ten to twenty days.

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From the Research Service, 1st Medical (Columbia) Division, Welfare Hospital, and the Department of Medicine, Columbia University College of Physicians and Surgeons.

1. Peters, J. P., and Eisenman, A. J.: The Serum Proteins in Diseases Not Primarily Affecting the Cardiovascular System or Kidneys, *Am. J. M. Sc.* **186**: 808, 1933.

2. Myers, W. K., and Keefer, C. S.: Relation of Plasma Proteins to Ascites and Edema in Cirrhosis of the Liver, *Arch. Int. Med.* **55**:349 (March) 1935.

3. Grabfield, G. P., and Prescott, B. S.: Nitrogen and Sulfur Metabolism in Bright's Disease: VIII. Effect of Ingestion of Urea on Nitrogen Excretion and Sulfur Partition in Nephrosis, Glomerulonephritis and Cirrhosis of Liver, *Arch. Int. Med.* **59**:823 (May) 1937.

4. Ling, S. M.: Changes in Serum Proteins in Undernutrition, *Chinese J. Physiol.* **5**:1, 1931.

5. Liu, S. H.; Chu, H. I.; Wang, S. H., and Chung, H. L.: Effect of Level and Quality of Protein Intake on Nitrogen Balance, Plasma Proteins and Edema, *Chinese J. Physiol.* **6**:73, 1932.

Madden and Whipple<sup>6</sup> found that when normal dogs were maintained on a low protein diet and subjected to prolonged plasmapheresis the serum proteins could be markedly reduced. However, the feeding of adequate protein quickly restored the low blood protein levels to normal.

Weech and Goettsch<sup>7</sup> found that regeneration of blood protein was rapid in normal dogs whose protein stores were depleted for relatively short periods (twenty-one days) by low protein feeding. However, blood protein regeneration was impaired when protein starvation was continued for longer periods (eighty-five days). "Extreme fatty infiltration and distended bile canaliculi" were observed in the livers of such animals. The authors suggested the possibility that there might be associated with these microscopic changes disturbances in hepatic function which could account for the abnormally slow regeneration of blood protein.

There is ample evidence that injury to the liver may affect protein metabolism. Kerr, Hurwitz and Whipple<sup>8</sup> have shown that in dogs with Eck fistulas or in those poisoned with chloroform or phosphorus the ability to form blood protein after plasmapheresis is impaired. Knutti, Erickson, Madden, Rekers and Whipple<sup>9</sup> recently confirmed this observation with respect to the Eck fistula dog. Furthermore, poisoning with carbon tetrachloride decreases the serum albumin.<sup>10</sup> Other authors have observed hypoalbuminemia in such diseases of the liver as acute catarrhal jaundice and toxic hepatitis,<sup>11</sup> and in simple atrophy of the liver in a child.<sup>12</sup>

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6. Madden, S. C., and Whipple, G. H.: Plasma Proteins: Their Source, Production and Utilization, *Physiol. Rev.* **20**:194, 1940.

7. Weech, A. A., and Goettsch, E.: Dietary Protein and the Regeneration of Serum Albumin, *Bull. Johns Hopkins Hosp.* **63**:154, 1938.

8. Kerr, W. J.; Hurwitz, S. H., and Whipple, G. H.: Regeneration of Serum Proteins: Liver Injury Alone; Liver Injury and Plasma Depletion; Eck Fistula Combined with Plasma Depletion, *Am. J. Physiol.* **47**:370, 1918.

9. Knutti, R. E.; Erickson, C. C.; Madden, S. C.; Rekers, P. E., and Whipple, G. H.: Liver Function and Blood Plasma Protein Formation: Normal and Eck Fistula Dogs, *J. Exper. Med.* **65**:455, 1937.

10. Erickson, C. C.; Heckel, G. P., and Knutti, R. E.: Blood Plasma Proteins as Influenced by Liver Injury Induced by Carbon Tetrachloride and Gum Acacia, *Am. J. Path.* **14**:537, 1938.

11. Wiener, H. J., and Wiener, R. E.: Plasma Proteins, *Arch. Int. Med.* **46**:236 (Aug.) 1930. Butt, H. R.; Snell, A. M., and Keys, A.: Plasma Proteins in Hepatic Disease: A Study of the Colloid Osmotic Pressure of Blood Serum and of Ascitic Fluid in Various Diseases of the Liver, *ibid.* **63**:143 (Jan.) 1939. Gray, S. J.: Colloidal Gold Reaction of Blood Serum in Diseases of the Liver, *ibid.* **65**:524 (March) 1940. Myers and Keefer.<sup>2</sup>

12. Thompson, W. H.; McQuarrie, I., and Bell, E. T.: Edema Associated with Hypogenesis of Serum Proteins and Atrophic Changes in the Liver with Studies of Water and Mineral Changes, *J. Pediat.* **9**:604, 1936.

From our own observations on patients with cirrhosis of the liver, it seems unlikely that the low serum albumin values in cases of this disease are due to simple protein starvation, although in many instances the diet before admission to the hospital may have been deficient in meat and dairy products.<sup>13</sup> Furthermore, after admission to the hospital many patients were fed 1.5 to 2 Gm. of protein per kilogram of body weight daily for weeks or months without the occurrence of a significant rise in the level of the serum albumin. These patients did not have diarrhea. Such findings are quite different from those for patients with starvation hypoproteinemia.<sup>14</sup> A further distinguishing feature between starvation hypoalbuminemia and the hypoalbuminemia associated with cirrhosis of the liver is that in the latter disease the globulin level may be high whereas in starvation hypoalbuminemia the globulin level is usually normal.

In order to determine whether the hypoalbuminemia occurring in cirrhosis of the liver is due to insufficient protein intake, to faulty gastrointestinal absorption or to faulty synthesis of serum albumin, nitrogen balance was studied in 5 patients with cirrhosis of the liver and ascites. The results show that these patients with hypoalbuminemia are in positive nitrogen balance, although there is no associated rise of serum albumin, and suggest impaired synthesis of serum albumin.

#### METHOD

Five patients with cirrhosis of the liver, ascites and hypoalbuminemia were studied. The ascites did not require paracentesis. All patients were confined to bed during the study periods. For patients 1, 2 and 3 (table 1) balance studies were made at approximately two week intervals for two, two and one month, respectively. For patients 4 and 5 (table 2) urinary nitrogen was determined daily for thirty-two and twenty-five days, respectively, the stools being collected for two forty-eight hour and two seventy-two hour periods in each case. The average of these determined values for fecal nitrogen was considered the daily fecal nitrogen content during the entire period of study (table 3). Urine was collected under xylene, and stools were collected in concentrated sulfuric acid. Determinations of urinary nitrogen were done in duplicate and determinations of fecal nitrogen were done in triplicate. All results were checked within 1 per cent.

The daily diets, which were composed of fresh meats, fruits and vegetables, dairy products and bread, contained approximately 280 Gm. of carbohydrate, 100 Gm. of fat and 100 Gm. of protein. A foreperiod of four to six weeks on such a diet preceded the balance studies in each case. The diets were weighed before and after meals and the protein content computed from tables.<sup>15</sup> The

13. Patek, A. J., Jr., and Post, J.: Treatment of Cirrhosis of the Liver by a Nutritious Diet and Supplements Rich in Vitamin B Complex, *J. Clin. Investigation* 20:481, 1941.

14. Ling.<sup>4</sup> Liu, Chu, Wang and Chung.<sup>5</sup>

15. Waller, D. S.: *Nutritive Value of Foods*, Ann Arbor, Mich., George Wahr, Publisher, 1936.

TABLE 1.—Nitrogen Balance in Three Patients with Cirrhosis of the Liver and Ascites

Patient No.	Date	Nitrogen Intake, Gm.	Urinary Nitro-gen, Gm.	Fecal Nitro-gen, Gm.	Nitrogen Balance, Gm.	Serum Albu-min, Gm. per 100 Cc.	Serum Glob-ulin, Gm. per 100 Cc.	Serum Nonprotein Nitrogen, Mg. per 100 Cc.	Comment
1	4/ 2/40	18.4	11.6	0.7	+ 6.1	2.8	5.4	35	Negro aged 45; history of intensive antisyphilitic treatment and alcoholism; severe jaundice and moderate ascites of 4 months' duration; hepatosplenomegaly; bromsulphalein dye retention 60 per cent in one-half hour; chronic bilateral pyelonephritis with albuminuria; slow diuresis
	4/ 3/40	16.9	11.7	0.7	+ 4.5				
	4/14/40*	14.9	8.6	0.9	+ 5.4				
	4/15/40*	15.9	6.6	0.9	+ 8.4				
	4/18/40	....	....	....	....	3.0	5.2	39	
	5/30/40	18.5	13.3	1.7	+ 3.5				
	5/31/40	15.7	12.7	1.7	+ 1.3				
2	6/ 1/40	....	....	....	....	2.4	4.3	38	White woman aged 50; marked alcoholism, with one episode of delirium tremens (November 1939); moderate ascites of 2 months' duration; many spider angiomas; bromsulphalein dye retention 69 per cent in one-half hour; urine normal; slow diuresis
	3/23/40	....	....	....	....				
	3/27/40	18.7	6.4	0.3	+12.0	2.8	4.0	35	
	3/28/40	20.0	7.7	0.3	+12.0				
	4/ 2/40	18.1	7.8	1.2	+ 9.1	2.5	4.7	23	
	4/ 3/40	17.9	8.8	1.2	+ 7.9				
	4/ 8/40	....	....	....	....	2.7	4.1	23	
	4/14/40*	14.2	8.5	1.4	+ 4.3				
	4/15/40*	13.5	8.8	1.4	+ 3.3				
	4/18/40	....	....	....	....	3.0	4.4	29	
	5/ 2/40	....	....	....	....	3.4	4.5	30	
3	5/30/40	19.5	12.9	2.5	....				White man aged 45; history of intensive antisyphilitic treatment; episode of hematemesis 2 months before study began treated with 3 transfusions, with marked improvement; moderate ascites of 1 month's duration; many spider angiomas; esophageal varices revealed by roentgen ray examination; bromsulphalein dye retention 30 per cent in one-half hour; urine normal; slow diuresis
	5/31/40	19.6	12.9	2.5	+ 4.2				
	6/ 4/40	....	....	....	....	3.2	3.7	27	
	3/14/40	....	....	....	....				
	3/15/40	20.0	11.4	0.9	....	3.2	3.1	28	
	4/ 2/40	20.3	10.9	2.4	+ 7.7				
	4/ 3/40	18.2	11.6	2.4	+ 7.0	3.1	3.2	27	
	4/ 8/40	....	....	....	+ 4.2				
	4/14/40*	16.5	3.4	0.9	+42.2	3.4	3.5	27	
	4/15/40*	15.9	7.8	0.9	+ 7.2				
	1/18/40	....	....	....	....	3.0	3.8	33	

\* No brewers' yeast was administered.

TABLE 2.—Nitrogen Balance in Two Patients with Cirrhosis of the Liver and Ascites

Date	Patient 4 *					Patient 5 †						
	Nitrogen Intake, Gm.	Urinary Nitrogen, Gm.	Nitrogen Balance, † Gm.	Serum Albumin, Gm. per 100 Cc.	Serum Globulin, Gm. per 100 Cc.	Serum Nonprotein Nitrogen, Mg. per 100 Cc.	Nitrogen Intake, Gm.	Urinary Nitrogen, Gm.	Nitrogen Balance, § Gm.	Serum Albumin, Gm. per 100 Cc.	Serum Globulin, Gm. per 100 Cc.	Serum Nonprotein Nitrogen, Mg. per 100 Cc.
9/ 5/40.....	16.1	9.7	+ 5.0	...	...	..	18.4	11.5	+ 5.0	3.2	4.2	25
9/ 6.....	13.5	14.2	— 3.1	...	...	..	17.3	11.7	+ 4.0	..	..	..
9/ 7.....	12.0	13.7	— 3.1	2.8	3.9	23	16.8	10.6	+ 4.6	..	..	..
9/ 8.....	13.5	12.1	0	...	...	..	18.9	10.6	+ 6.7	..	..	..
9/ 9.....	13.3	15.6	— 3.7	...	...	..	15.4	..	..	..	..	..
9/10.....	15.6	9.0	+ 5.2	...	...	..	16.6	12.2	+ 2.8	..	..	..
9/11.....	19.3	12.1	+ 5.8	...	...	..	12.8	9.5	+ 1.7	..	..	..
9/12.....	18.1	11.6	+ 5.1	...	...	..	16.9	9.6	+ 5.7	..	..	..
9/13.....	18.3	12.3	+ 4.6	...	...	..	16.2	8.6	+ 6.0	..	..	..
9/14.....	19.9	10.2	+ 8.3	2.7	4.0	27	14.4	10.0	+ 2.8	..	..	..
9/15.....	18.6	11.4	+ 5.8	...	...	..	17.3	15.4	+ 0.3	3.2	4.3	27
9/16.....	19.4	6.7	+11.3	...	...	..	14.7	10.7	+ 2.4	..	..	..
9/17.....	14.6	11.4	+ 1.8	...	...	..	16.5	10.7	+ 4.2	..	..	..
9/18.....	18.9	16.3	+ 1.2	...	...	..	18.5	12.2	+ 4.7	..	..	..
9/19.....	19.4	15.5	+ 2.5	...	...	..	14.5	12.1	+ 0.8	..	..	..
9/20.....	16.7	8.5	+ 6.8	...	...	..	17.7	10.3	+ 5.8	..	..	..
9/21.....	17.0	11.7	+ 3.9	...	...	..	16.3	10.0	+ 4.7	..	..	..
9/22.....	20.9	11.4	+ 8.1	...	...	..	20.3	..	..	..	..	..
9/23.....	17.2	13.3	+ 2.5	2.4	3.6	28	17.7	12.9	+ 3.2	3.3	3.4	29
9/24.....	19.3	11.3	+ 6.9	...	...	..	17.4	11.1	+ 4.7	..	..	..
9/25.....	18.6	11.6	+ 5.6	...	...	..	21.0	13.9	+ 5.5	..	..	..
9/26.....	19.1	12.4	+ 5.3	...	...	..	16.5	12.6	+ 2.3	..	..	..
9/27.....	23.8	11.3	+11.1	...	...	..	19.0	13.9	+ 3.5	..	..	..
9/28.....	19.4	11.7	+ 6.3	...	...	..	17.6	9.9	+ 6.1	..	..	..
9/29.....	21.8	13.2	+ 7.2	...	...	..	21.4	10.7	+ 9.1	..	..	..
9/30.....	18.5	9.2	+ 7.9	...	...	..	19.2	11.8	+ 5.8	3.6	4.4	32
10/ 1.....	15.7	12.7	+ 1.6	...	...	..	18.1	11.8	+ 4.7	..	..	..
10/ 2.....	18.2	13.4	+ 4.0	...	...	..	..	..	..	..	..	..
10/ 3.....	18.0	9.0	+ 7.6	2.5	3.7	23	..	..	..	..	..	..
10/ 4.....	17.8	17.4	— 0.6	...	...	..	..	..	..	..	..	..
10/ 5.....	17.8	14.3	+ 2.1	...	...	..	..	..	..	..	..	..
10/ 6.....	14.3	10.1	+ 2.8	...	...	..	..	..	..	..	..	..

\* A white man aged 50 with a history of extreme alcoholism, one episode of severe peripheral neuritis 6 months before study was begun, appreciable ascites of 3 months' duration, severe jaundice, hepatosplenomegaly, numerous spider angiomas, retention of 80% of an injection of bromsulphalein, normal urine and slow diuresis.

† A Negro aged 36 with a history of extreme alcoholism, severe ascites of 3 months' duration, bromsulphalein dye retention 40 per cent in one-half hour, normal urine and slow diuresis.

‡ Average excretion of fecal nitrogen = 1.4 Gm. per 24 hours (see table 4).

§ Average excretion of fecal nitrogen = 1.6 Gm. per 24 hours (see table 4).

factor 1/6.25 was used for conversion to nitrogen. The accuracy of the food tables used was checked by chemical analyses of six sample diets (table 4). A sample diet was placed in a Waring mixer for two to three hours, and portions of the resulting homogeneous mixture were analyzed in triplicate and checked within less than 1 per cent. Except where otherwise noted the patients received 40 to 60 Gm. of brewers' yeast daily, in addition to the diet. The nitrogen content of this yeast was determined as 8.5 per cent. The micro-Kjeldahl method for nitrogen determination was employed throughout the studies.

TABLE 3.—*Excretion of Fecal Nitrogen by Patients 4 and 5*

	Date	Fecal Nitrogen, Gm.
Patient 4	9/14 - 9/16.....	2.0
	9/21 - 9/23.....	3.0
	9/29 -10/ 2.....	3.9
	10/ 5 -10/ 8.....	5.4
	Average.....	1.4 Gm. per 24 hr.
Patient 5	9/ 6 - 9/ 8.....	3.4
	9/14 - 9/16.....	4.4
	9/21 - 9/24.....	4.5
	9/29 -10/ 2.....	3.6
	Average.....	1.6 Gm. per 24 hr.

TABLE 4.—*Comparison of the Calculated and Determined Nitrogen Contents of Six Sample Diets*

Calculated Amount of Nitrogen	Determined Amount of Nitrogen
4.10 Gm.	4.10 Gm.
7.63 Gm.	8.50 Gm.
3.18 Gm.	3.19 Gm.
5.56 Gm.	6.87 Gm.
3.18 Gm.	3.23 Gm.
6.43 Gm.	7.63 Gm.

## RESULTS

The data for the 5 patients studied (tables 1 through 4) show that relatively normal amounts of nitrogen, 0.3 to 2.5 Gm. per twenty-four hours, were being lost in the stools. Therefore it is concluded that the patients had no defect in the absorption of protein from the intestinal tract. These results confirm those of Myers and Keefer.<sup>2</sup> Furthermore, they indicate that the patients were in positive nitrogen balance, since the nitrogen intake exceeded the nitrogen output. Such findings indicate that the patients were in a state of partial protein depletion, as suggested by Peters and Eisenman.<sup>1</sup> However, since the nonprotein nitrogen of the blood and the serum proteins, particularly the serum albumin, remained essentially unchanged and since there was no constant drain

of protein by abdominal paracentesis, it appears that nitrogen was being stored, probably as body protein. In other words, there is no apparent tendency for the serum proteins to reflect this positive nitrogen balance.

This ability of the body to retain protein from the food and its failure to synthesize serum proteins may be illustrated by the following examples:

Patient 5 showed a rise in serum albumin from 3.2 to 3.6 Gm. per hundred cubic centimeters during the period of four weeks, an increase of approximately 13 Gm. of circulating albumin. However, during this time the patient retained the equivalent of 657 Gm. of protein as nitrogen. Patient 4 showed a slight decrease in the serum albumin from 2.8 to 2.5 Gm. per hundred cubic centimeters during the four and a half weeks of study, but retained the equivalent of 849 Gm. of protein as nitrogen.

This type of balance pattern is quite different from that seen in cases of nutritional hypoproteinemia. In the latter the level of the serum proteins, particularly that of the serum albumin, rises fairly rapidly when protein is fed.<sup>14</sup> Whipple<sup>16</sup> has shown that there normally exists a ready exchange between the body protein stores and the blood proteins and that the latter are reduced only after body protein stores are depleted. When protein is made available to the animal, the first response is a rise in the blood protein level. It appears from our data that in the patient with cirrhosis of the liver the restoration of the serum albumin to normal is delayed when protein is made available. The retained nitrogen is apparently converted to body protein and not to blood protein, a change which suggests faulty synthesis of serum albumin.

#### SUMMARY AND CONCLUSIONS

Nitrogen balance studies were made on 5 patients with cirrhosis of the liver, ascites and reduced serum albumin.

Although the patients remained in positive nitrogen balance during the periods of high protein feeding, there was no correlated rise in the level of the serum albumin. In this respect these patients differ from persons with simple protein starvation.

The data recorded here indicate that patients with cirrhosis of the liver absorb and retain food protein. The evidence suggests that the mechanism for the synthesis of serum albumin is impaired.

Miss Josephine Henneberger gave technical assistance.

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16. Whipple, G. H.: Protein Production and Exchange in the Body, Including Hemoglobin, Plasma Protein and Cell Protein, *Am. J. M. Sc.* **196**:609, 1938.



# TORULA MENINGITIS

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AND

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We report a case of fatal torula meningitis complicating Hodgkin's disease.

## REPORT OF A CASE

The patient was an American-born man aged 39 who was referred to the Collis P. Huntington Memorial Hospital for treatment of "reticulum cell sarcoma" of the neck and the mediastinum. This diagnosis had been made at another hospital on the basis of a biopsy of a right supraclavicular node and a widened mediastinal shadow in a roentgenogram. Symptoms of easy fatigability, loss of appetite, susceptibility to colds and rheumatoid pains had been present for about one year, but the most distressing and urgent symptom, severe occipitofrontal headaches, was of shorter duration, a little over one month. Projectile vomiting had accompanied some of these attacks of headache, and an irregular fever, with a temperature up to 103 F., had been noted during one of these occasions. The only point of possible interest in the past history was a deep injury to the nose resulting from a fall on an upright stick in 1933.

At the time of admission, the patient was well developed but had evidently lost a great deal of weight. There was no marked enlargement of peripheral lymph nodes. Mediastinal tumor was suggested by a widening and an increased density of the upper portion of the mediastinum, detectable both by percussion and in the roentgenograms. The teeth were carious, and the tonsils had a granular appearance but were not enlarged. Neurologic examination gave no clue to his headaches. The reflexes were sluggish. Impairment of vision was striking, the patient being able to read only large newspaper print. Bilateral papilledema, with an elevation of 1 D., and wasting of interosseous muscles and of the thenar eminences of the hands were present. Except for leukocytosis, with a white cell count of 20,350 per cubic millimeter, the blood count was not remarkable. Roentgenograms showed diffuse calcification in the choroid plexuses. A lumbar puncture disclosed fluid under normal pressure, with no unusual cell content, a negative Wassermann reaction and a colloidal gold curve of 0001121100. Super-voltage radiation was given to the anterior portions of the mediastinum and the abdomen in equal amounts of 800 r, with relief of nausea and vomiting. Shortly thereafter, 740 r directed to the side of the head through a 15 by 15 centimeter portal seemed to lessen the severity of the headaches, and there were some improvement in vision and reduction of papilledema.

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For three months the patient did not suffer any appreciable discomfort, but weakness and headaches gradually returned. The headaches became progressively worse and were most troublesome at night. Projectile vomiting in the morning became distressing. Because of the severe headaches and vomiting, the patient was admitted to the hospital a second time, nine months after his first admission and radiation treatments. At this time examination revealed the same physical findings noted previously, with additional nystagmoid movements on looking to the right, as well as some loss of coordination. Lymph nodes in the right cervical chain were definitely enlarged, and the spleen was palpable. Lumbar puncture revealed normal dynamics of the cerebrospinal fluid, an increase in the cell count to 196 per cubic millimeter, a total protein content of 200 mg. per hundred cubic centimeters and a colloidal gold curve of 0000112110. A culture of the fluid was negative for growth, and a guinea pig inoculated with the fluid failed to show any lesions after twenty days. Histologic examination of a cervical node disclosed Hodgkin's disease. In view of the subjective improvement following the first supervoltage roentgen irradiation to the head, a second series of twelve daily treatments, totaling 800 r, was given. After the roentgen irradiation there was again some relief of the headaches but less than that which followed the first irradiation nine months before. However, an examination of cerebrospinal fluid showed a reduction of the cell count to 74 cells per cubic millimeter, with a further reduction one month later to 22 cells per cubic millimeter. The other findings for the cerebrospinal fluid were the same as on the first admission, and cultures did not show any growth. In addition, 1,200 r supervoltage radiation was directed to the mediastinum and 600 r high voltage radiation to the right supraclavicular region. This was followed by reduction in size of the lymph nodes and the spleen. The patient felt improved and returned home.

After this second series of radiation treatments, the relief from symptoms was less complete and of shorter duration, and the patient was readmitted, after a five month interval, for what proved to be his last series of treatments. Examination at this time disclosed his increasingly poorer condition, for he was completely disoriented, emaciated and weak. The spleen was definitely enlarged, as were the lymph nodes in the left supraclavicular area. The left pupil was dilated, and ophthalmoscopic examination revealed choroiditis on that side. An encephalogram disclosed nothing remarkable. Lumbar puncture still showed normal dynamics, but the cell count had increased to 38 per cubic millimeter of cerebrospinal fluid and continued to rise to 181, as shown in the last examination, done one month later. Otherwise, the cerebrospinal fluid was unchanged, and cultures were still negative for growth. The patient was given 500 r supervoltage radiation to his head in two treatments with no noticeable effect. He also received 600 r high voltage radiation to the left supraclavicular area and 900 r supervoltage radiation to the left upper portion of the abdomen, including the spleen. There was a reduction in the size of the lymphoid tumors, but otherwise no improvement. The blood picture, which had been normal on entry, was characterized by a red cell count of 2,350,000 per cubic millimeter and a hemoglobin concentration of 44 per cent (Sahli); the progressive anemia continued in spite of a transfusion of 500 cc. of citrated blood. The leukocytes had remained fairly constant, around 10,000 per cubic millimeter, with a differential count of 81 per cent neutrophils, 10 per cent lymphocytes, 7 per cent monocytes, 1 per cent eosinophils and 1 per cent basophils, but the leukocytes were reduced to 4,500 per cubic millimeter, with a comparable differential count. The results of urinalysis had been essentially negative but began to show terminal pyuria. The decline was rapid, with development of coma during the last few days, and death occurred from respira-

tory failure, eighteen months after the onset of severe neurologic symptoms and thirty months after the onset of symptoms referable to the known lymphomatous lesions.

To summarize, the clinical course had two distinct aspects: The first was malignant lymphoid tumor which involved the cervical and mediastinal nodes, with weakness, loss of weight and vague symptoms that began two and a half years before death. The second, more striking, group of symptoms was related to an intracranial involvement of only eighteen months' duration. In the absence of definite evidence to the contrary and in spite of its rarity, the entire clinical picture was ascribed to the proved malignant lymphoid tumors.

At necropsy two distinct gross pathologic entities were found: (a) a slight inflammatory reaction in the meninges of the brain, spinal cord and ependyma and (b) discrete fibrous and granular nodules in various organs, interpreted as evidence of Hodgkin's disease.

The dura of the brain was normal, but the leptomeninges of the brain were everywhere edematous and slightly cloudy with more definite opacity over the principal fissures and over the brain stem. The brain substance was normal in every respect, there being no evidence of extension of inflammation from the pia-arachnoid. Uniform, finely granular ependymitis was present in all the ventricles; the choroid plexuses were firm and covered by a dull white membrane. The dura of the entire cord was attached to the pia by fairly tenacious, fine adhesions. The substance of the cord was normal.

Microscopic examination of the brain and cord disclosed diffuse leptomeningitis, most exuberant around the large vessels, consisting of a granulomatous reaction to a yeastlike organism, *Torula*. Usually the response excited by the presence of these organisms is simply a migration of endothelial leukocytes, although lymphocytes, eosinophils and polymorphonuclears may play a minor role. In our case only rare lymphocytes were seen among the large numbers of endothelial leukocytes which actively phagocytosed the organism. Large giant cells formed by the fusion of leukocytes and filled with torulas, many of which were partly degenerated, gave a foamy appearance to the exudate. The infection had extended along some of the small vessels into the substance of the brain and had invaded adjacent brain tissue in a few minute foci. Some of these foci had undergone dissolution, which produced microscopic cavities. A few of the spinal nerves were likewise invaded by the organism.

Although large numbers of endothelial leukocytes were present, there were almost as many torula organisms lying free in the meshes of the edematous meninges. They were for the most part well preserved, and a few were in the process of budding, but several showed slight changes in contour and staining properties that suggested early degeneration. Aside from the migration of endothelial leukocytes and a few lymphocytes, there had been no appreciable response to the presence of the organism. Only slight thickening of the fibrous elements of the leptomeninges, without distinct evidence of proliferation, was noted.

The concomitant pathologic process, consisting of discrete granular and fibrous lesions, was evident (a) in the cervical, supraclavicular, axillary, inguinal and pulmonary hilar lymph nodes, producing moderate enlargement and uniform structure; (b) throughout the parenchyma of both lungs as granular, but partially fibrous, nodules 1 to 2 cm. in diameter; (c) in the center of the left lobe of the liver as a single, solitary nodule with irregular streaked edges, a lesion more characteristic of scirrhus carcinoma than of Hodgkin's disease; (d) in a large,

530 Gm. spleen as numerous, slightly elevated, granular, yellow nodules averaging 2.5 cm. in diameter and separated by bands of dark purple pulp, and (c) in the lumbar vertebral marrow as scattered yellowish, nondescript foci under 1 cm. in diameter.

Histologically, these lesions differed from those observed during the second biopsy, made at the Huntington Memorial Hospital six months before death, by a greater predominance of fibrosis and reduction in cells, chiefly lymphocytes, eosinophils, plasma cells, multinuclear giant cells and rare Sternberg cells. The

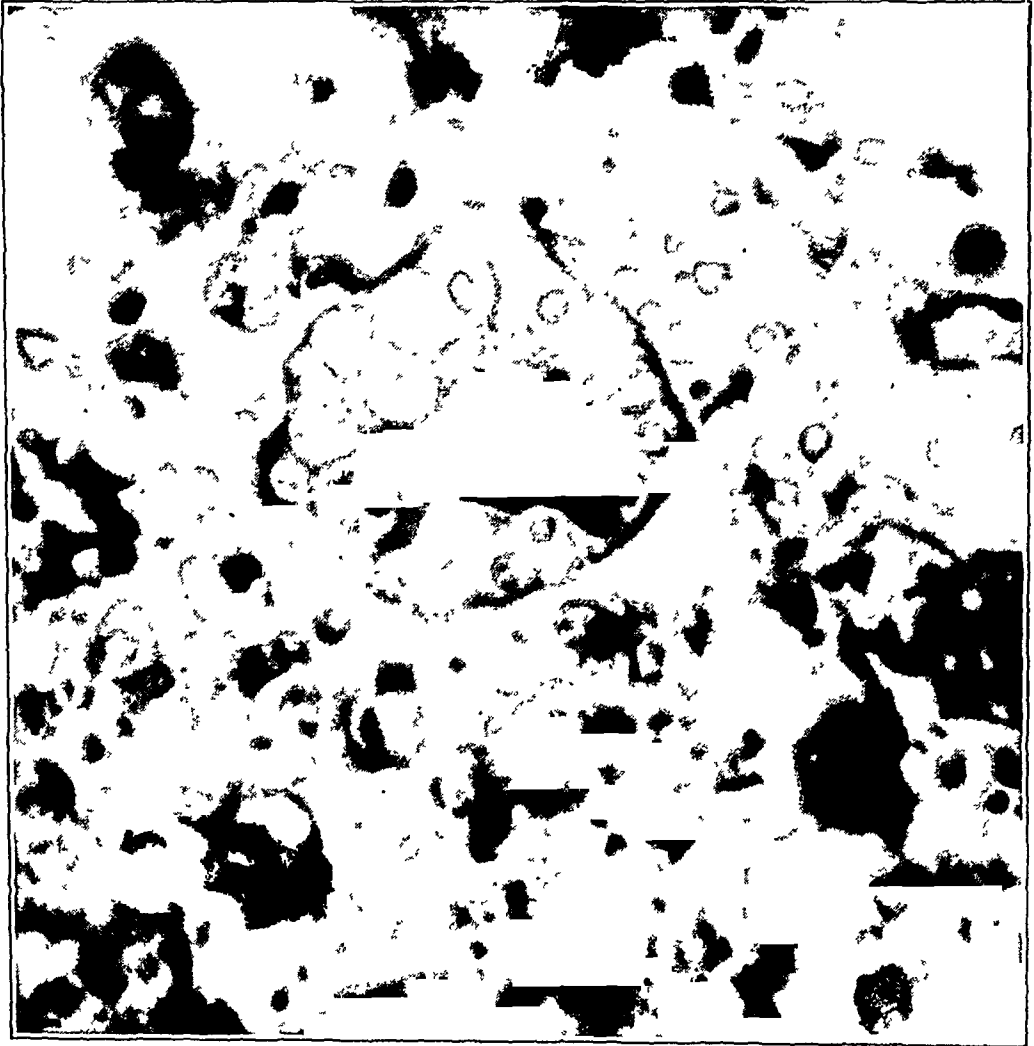


Fig. 1.—A section of the leptomeninges showing a large giant cell with multiple, deeply staining, clumped nuclei in the center and engulfed torula organisms in the periphery. Torulas are also visible lying free in tissue spaces, as well as in single phagocytes.  $\times 600$ .

lesions most characteristic of Hodgkin's disease were in the lymph nodes, liver, spleen and bone marrow.

Some of the nodules in the lung parenchyma appeared less typical, and, in view of the recorded cases of torula lesions having been misinterpreted as Hodgkin's disease, and also because the respiratory tract is reported to be the portal of entry for the organism, a more careful study was made of these lesions. Many sections stained by the Gram-Weigert method and with phosphotungstic acid

hematoxylin and hematoxylin and eosin were fruitlessly searched for the organism, although the appearance of a few vacuolated, phagocytic cells suggested its presence. In connection with his aid in the preparation of the monograph by Stoddard and Cutler,<sup>1</sup> Dr. S. Burt Wolbach had found Masson's aniline blue stain most helpful in demonstrating *Torula*. With the use of this stain, organisms could be seen in a few phagocytic cells in the periphery of the pulmonary nodules. Their identity was confirmed by Dr. Shields Warren,<sup>2</sup> so that we can confidently say that the pulmonary lesions are, at least in part, a reaction to the yeast and the lung may

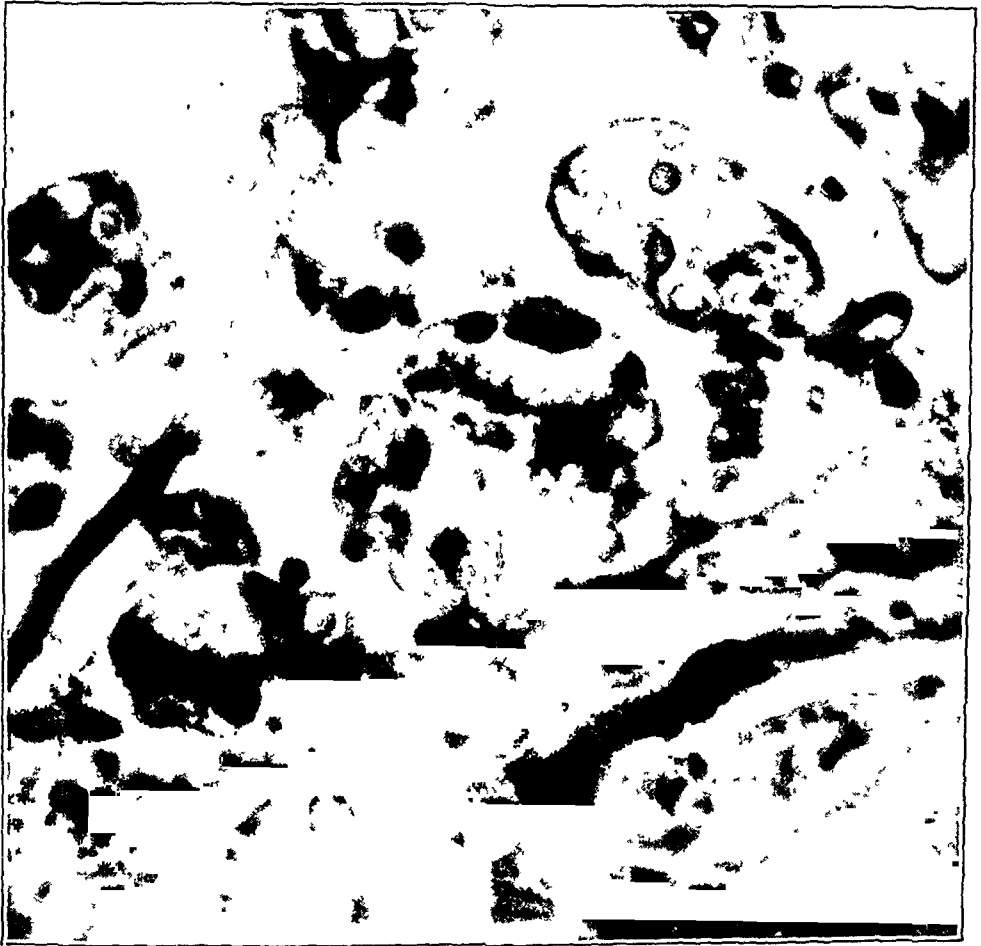


Fig. 2.—Perivascular infiltration of phagocytic cells and organisms.  $\times 600$ .

have been a portal of entry in this case. The scarcity of organisms in parenchymatous organs has been ascribed to the exuberant reaction and fibroblastic proliferation that obscures them and also causes their degeneration. More often *Torula* produces a large caseous lesion in the lung, but Rappaport and Kaplan<sup>3</sup> reported multiple small fibrous foci similar to those seen in this case.

1. Stoddard, J. L., and Cutler, E. C.: *Torula Infection in Man*, Monograph 6, Rockefeller Institute for Medical Research, 1916.

2. Pathologist to the Collis P. Huntington Memorial Hospital.

3. Rappaport, B. Z., and Kaplan, B.: Generalized *Torula* Mycosis, *Arch. Path.* 1:720 (May) 1926.

## COMMENT

The first inclusive and useful report of torula meningitis in man was made by Stoddard and Cutler,<sup>1</sup> in 1916. In a later (1931) extensive review of the subject, Freeman<sup>4</sup> accepted 43 cases as authentic. Levin<sup>5</sup> reviewed the subject in 1937 and added 14 cases reported in the literature after Freeman's article, as well as 2 cases of his own. Binford<sup>6</sup> (1930) tabulated 14 cases reported subsequent to Levin's review and added 1 case of his own. Wade and Stevenson<sup>7</sup> recently (1941) reported 1 case, and Stiles and Curtiss<sup>8</sup> added still another. To a total of 77 cases recorded in the literature we add a seventy-eighth. One feature notable in a review of the subject is the frequency with which Hodgkin's disease and torula meningitis are associated. Wade and Stevenson<sup>7</sup> cited 4 cases of coincident lymphomatosis, and Mallory<sup>9</sup> stated that he had personally observed 5 instances. In 7 of these 9 cases the lymphomatous lesions were those of Hodgkin's disease. Mallory<sup>9</sup> further referred (1934) to an unpublished manuscript mentioning about a dozen cases of associated torula infection and Hodgkin's disease, although we find no report to date containing this number of cases. Mallory<sup>9</sup> remarked: "The coincidence is much too striking to be purely a matter of chance. It is not so close as the coincidence of tuberculosis and Hodgkin's disease, but it certainly approaches it."

Torula, a yeastlike organism, is widely distributed throughout nature and is only rarely pathogenic for man. It differs from a true yeast in that it does not produce endospores and forms mycelium only under certain cultural conditions (Ball<sup>10</sup>). The organisms were, for the most part, well preserved in the leptomeninges in our case. Some were seen in the process of budding, which is the characteristic method of reproduction. They were 2 to 14 microns in diameter, with a central round body and a mucoid capsule that did not take ordinary stains but was apparent because of its distinct outer membrane. Although there are vagaries of staining, Mallory's aniline blue stains the organisms orange

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4. Freeman, W.: Torula Infection of the Central Nervous System, *J. f. Psychol. u. Neurol.* **43**:236, 1931.

5. Levin, E. A.: Torula Infection of the Central Nervous System, *Arch. Int. Med.* **59**:667 (April) 1937.

6. Binford, C. H.: Torulosis of the Central Nervous System: Review of Recent Literature and Report of a Case, *Am. J. Clin. Path.* **11**:242, 1941.

7. Wade, L. J., and Stevenson, L. D.: Torula Infection, *Yale J. Biol. & Med.* **13**:467, 1941.

8. Stiles, W. W., and Curtiss, A. N.: Torula Meningoencephalitis, *J. A. M. A.* **116**:1633 (April 12) 1941.

9. Torula Meningitis: Lymphoblastoma, Hodgkin's Type, Cabot Case 20241, *New England J. Med.* **210**:1291, 1934.

10. Ball, H. A.: Human Torula Infections: Review; Report of Cases, *California & West. Med.* **32**:338, 1930.

and the capsule blue. There appear to be several types or strains, which vary in size, in ease of cultivation and in pathogenicity for animals.

The effect of the organism, judging from reports in the literature, is more commonly the production of focal granulomatous lesions that grossly resemble those of tuberculosis. In our case the involvement was more diffuse, with edema of the leptomeninges and a cellular exudate consisting primarily of endothelial leukocytes that engulfed the organism and often coalesced to form giant cells. The lymphocytes, plasma cells and granulocytes, often reported present, were less prominent in our case. There was some extension of reaction along vascular sheaths into the brain substance but no evidence of the marked cystic process that has been described by some as giving a grossly visible "soap bubble" effect. The variability in pathologic processes has been related to the strain of organism; those with thicker capsules are supposedly accompanied by more cyst formation, while the thinner-capsuled organisms incite more of a microglial reaction. The organism appears to have little if any toxic action but acts more as a foreign body than as an infectious agent.

Little is known of the clinical course, especially in its early stages, since the condition is rarely diagnosed until meningitis is well established. The portal of entry is believed to be the respiratory tract, but the interval that precedes the onset of manifestations of cerebral involvement is not known. Signs and symptoms of increased intracranial pressure have an insidious onset but become progressively more severe, with short periods of remission. The first symptom is severe headache, which is later accompanied by projectile vomiting and increasing weakness. Coma or occasional convulsions occur late, and death is usually due to respiratory failure. Spread of the disease is by embolic dissemination, and organisms may be cultivated from the blood and the urine. Although torula organisms have been found in almost every organ at one time or another, such involvement, with rare exceptions, is usually secondary to the meningitis.

The possible presence of torula meningitis must be considered in all cases of slowly progressive meningeal irritation and increased intracranial pressure after the diagnosis of tuberculosis, syphilis and tumor of the brain have been excluded. The greatest help is from examination of the spinal fluid, which may appear clear, turbid or gelatinous, with an increase in pressure up to 700 cm. of water. The cell count is increased, with a predominance of lymphocytes. Torulas are often mistaken for red blood cells or lymphocytes but may be observed best in a hanging drop preparation and are most distinctive when seen engulfed by phagocytic cells. The proteins are increased, and the Pandy reaction for globulins is positive. The colloidal gold curve shows a midzone rise or occasionally may be of the paretic type. Culture of organisms may be

difficult, but growth should occur in carbohydrate mediums at room temperature. Cultures were repeatedly negative for *Torula* in our case and also in another case recently studied by Dr. Warren. If one judges by the case reports in the literature, the demonstration of organisms by culture is more difficult in cases in which the infection is of longer duration. Two of the most recently reported cases are examples of this. Binford<sup>6</sup> reported a case with a clinical course similar to that in ours and in which only 1 of 7 centrifuged specimens of cerebrospinal fluid yielded the organism either by culture or by microscopic examination, although injections into animals were successfully made with 3 different samples of fluid in which no organisms were seen or cultured. The case reported by Stiles and Curtiss<sup>8</sup> is the exact converse, for in it the illness ran an acute course, with death occurring on the twenty-fifth day after the onset of symptoms; the organism was cultured from the cerebrospinal fluid, as well as from the blood, from the first specimens taken at the end of the first week. Animal inoculations usually have been made intraperitoneally or intranasally into mice and rats; the guinea pig was used in our case, as well as in others reported recently.

The most definite diagnostic procedure is reported to be a biopsy of the meninges, particularly of tissue overlying a sulcus; however, care must be taken to obtain representative tissue and not the more accessible necrotic, membranous exudate in which the organisms are disintegrated and not demonstrable.

All treatment has been ineffective in 100 per cent of the cases, and death usually occurs within sixteen months after the onset of definite symptoms. The most complete therapeutic studies are accredited to Shapiro and Neal,<sup>11</sup> who kept their patient alive six months after a diagnosis of torulosis was made. They expressed the belief that the most effective palliative measure is the lumbar puncture, which keeps down the increasing intracranial pressure. In their case they performed 133 punctures. They later found acriflavine in a dilution of 1:10,000 to be the only substance that was inhibitory within therapeutic limits of dosage. There have been no reports of a clinical trial, but, in view of the invariably fatal course of this disease, the physicians at the New England Deaconess Hospital decided to try it in 1 case.<sup>12</sup> In this case the diagnosis of torulosis was suspected by Dr. Warren on examination of necrotic membranous material removed during a suboccipital exploration and was confirmed by demonstration of the organisms in the spinal fluid by observation in a hanging drop preparation, as well as by recovery of torulas from an inguinal abscess of a guinea pig inoculated

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11. Shapiro, L. L., and Neal, J. B.: *Torula Meningitis*, Arch. Neurol. & Psychiat. **13**:174 (Feb.) 1925.

12. The patient had been admitted to the New England Deaconess Hospital in the service of Dr. G. H. Horrax, of the Lahey Clinic.



intraperitoneally. However, the patient was already moribund when the treatment was started, and no response was observed to daily intrathecal administration of 42 cc. of acriflavine hydrochloride in a dilution of 1 : 10,000 after removal of 60 cc. of spinal fluid for seven days just before death. It would seem advisable to try this only known therapeutic possibility in a case in which this invariably fatal disease is in an earlier stage.

#### SUMMARY

The characteristic features of this case of torula leptomeningitis are the insidious onset and the intermittent but progressive course, going on to a fatal termination. The increasing intracranial involvement caused the following consecutive manifestations: severe headaches; visual, sensory and motor disturbances; weakness; projectile vomiting; disorientation; coma, and respiratory failure.

The interesting features of this case are the occurrence of the meningitis as a complication of Hodgkin's disease and the effect of the roentgen ray treatments to the head. This is the eighth reported case of associated Hodgkin's disease and torula meningitis. The marked reduction in cells in the cerebrospinal fluid is the only positive evidence of the effect of roentgen therapy, but it does not indicate whether it was harmful or beneficial except that our patient survived eighteen months after the first severe symptoms; for the most part he was ambulatory and in relative comfort. The usual course is one of severe symptoms and death within six months.

A review of the literature indicates that a diagnosis of torulosis is to be suspected in cases of otherwise unaccountable progressive intracranial disease. Confirmation is obtained by studies of the spinal fluid, with identification of the organism either by culture or by animal inoculation. A biopsy of representative tissue from the meninges will disclose the specific lesions.

The only undoubtedly beneficial therapeutic procedure appears to be repeated withdrawals of spinal fluid to promote drainage and decrease intracranial pressure. The use of acriflavine hydrochloride intrathecally may offer some possible curative effect in cases of this invariably fatal disease.

# ABSORPTION OF INTRACUTANEOUSLY INJECTED SOLUTIONS OF DEXTROSE AND SODIUM CHLORIDE

COMPARISON OF ABSORPTION TIMES FOR DIABETIC AND FOR  
NONDIABETIC SUBJECTS

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The behavior of dextrose and electrolytes in the tissues of persons, with diabetes is of considerable interest. Seelig<sup>1</sup> has recently reported on the response of diabetic patients to intradermal tests with a solution of sodium chloride and 0.1 per cent dextrose. He found an increased "avidity" of the skin for dextrose in the diabetic as compared with the nondiabetic patient. McClure and Aldrich,<sup>2</sup> Petersen and Levinson<sup>3</sup> and others have reported on the intracutaneous wheal as a measure of permeability in persons with nephritis as well as in normal subjects. There has been a lack of controlled studies on cellular permeability as measured by the absorption time of various solutions in the diabetic as compared with the nondiabetic, so-called normal subject.

The results of a preliminary study, based on the method of Seelig,<sup>1</sup> suggested that the test may be of value, first, in studying differences in absorption in patients with uncontrolled diabetes as compared with absorption in patients whose diabetes is "controlled," and, second, in measuring the transport of fluids within the tissues. Therefore two groups of patients were studied, one group with glycosuria and an elevated value for blood sugar and a second group without glycosuria and with a more normal value for blood sugar. The results for both groups were compared with those obtained for a group of persons in apparently good health who may be considered "normal." A smaller

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From the Department of Medicine, the University of Illinois College of Medicine.

1. Seelig, S. F.: Intradermal Skin Tests in Diabetes Mellitus, *Guy's Hosp. Rep.* **88**:210 (April) 1938.

2. McClure, W. B., and Aldrich, C. A.: Time Required for Disappearance of Intradermically Injected Salt Solution, *J. A. M. A.* **81**:293 (July 28) 1923. Aldrich, C. A., and McClure, W. B.: The Intradermal Salt Solution Test: II. Its Prognostic Value in Nephritis with Generalized Edema, *ibid.* **82**:1425 (May 3) 1924.

3. Petersen, W. F., and Levinson, S. A.: Skin Reactions, Blood Chemistry and Physical Status of "Normal" Men and of Clinical Patients, *Arch. Path.* **9**:151 (Jan., pt. 2) 1930.

group of patients with uncontrolled diabetes were studied at frequent intervals until they were brought under control.

The concentrations of substances chosen were the same as those reported by Seelig because they represent the average normal concentrations in the circulating blood. Because of the great difference in the osmotic pressure of an 0.85 per cent solution of sodium chloride and a 0.1 per cent solution of dextrose, the following solutions were prepared in order to determine the influence of the osmotic pressure on the rate of absorption. Each series of tests consisted of the injection of 0.5 cc. of each of these four solutions:

Solutions	Osmotic Pressure, Atmosphere
5% dextrose	6.22
0.85% sodium chloride	6.35
0.1 % dextrose	0.12
0.1 % dextrose in 0.85% sodium chloride	6.47

In order to study the absorption rates of solutions of compounds of larger molecular size and different arrangement, solutions of inulin and urea were added. The inulin was immediately discarded as being too irritating, while a 1.7 per cent solution of urea, with approximately the same osmotic tension as the 5 per cent solution of dextrose, was employed in smaller series of normal and diabetic subjects.

The technic of injections and the method of reading the end point were as follows: The needle was inserted superficially in such a manner that the lumen was visible through the skin; then 0.5 cc. of solution was injected. With slight pressure a distinct area of blanching may be clearly delineated at the site of injection. The fluid was assumed to be absorbed when the area of blanching had disappeared. This method was found to be more satisfactory than the method of palpation previously described.<sup>2</sup> The site of injection was the volar surface of the forearm. The same forearm was used repeatedly in tests on the same subject because differences in the absorption rates greater than those attributable to error were found in one forearm as compared with the other. McClure and Aldrich<sup>2</sup> have previously reported differences in the absorption rates in the upper and the lower extremity.

In order to obtain a measure of the accuracy of the technic, a series of twenty-four duplicate injections were made. In 62 per cent the error of reading was 1 minute or less, while in 75 per cent the error was 3 minutes or less.

The results of 143 observations on 45 diabetic patients and of 30 observations on 25 normal subjects have been summarized in table 1.

Charts 1, 2 and 3 were prepared in order to show both the range of variation of absorption times and the relation of the absorption

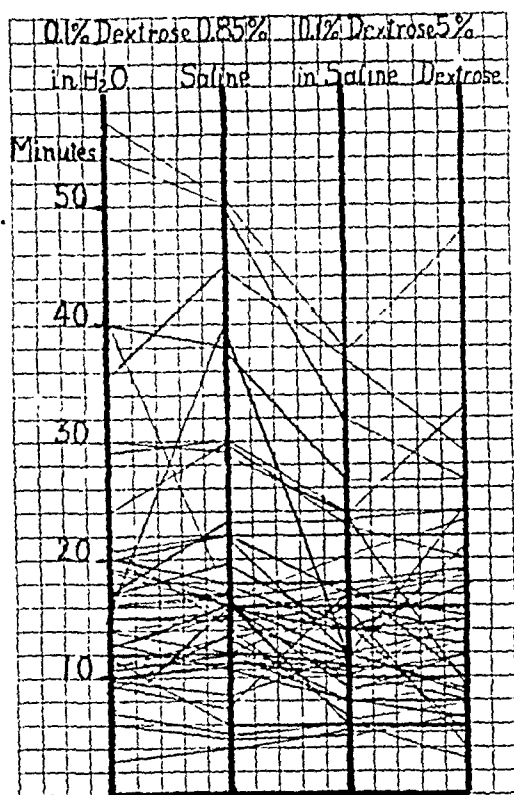


Chart 1.—Absorption times of intracutaneous injections of solutions of dextrose and sodium chloride for patients with uncontrolled diabetes.

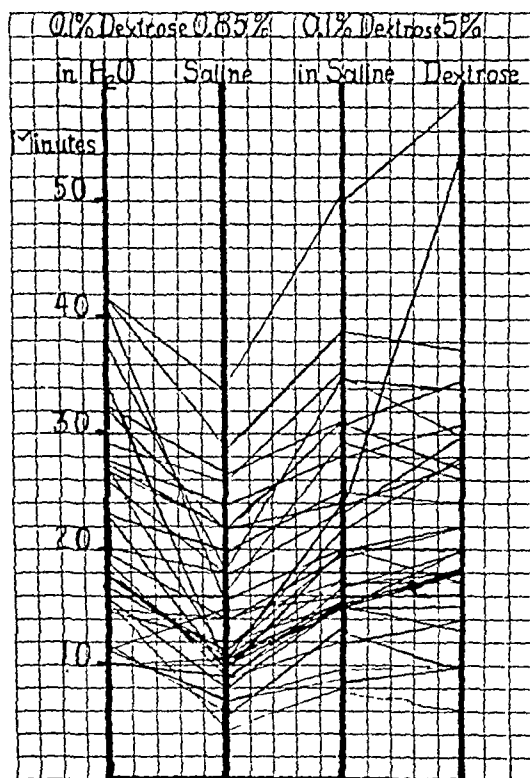


Chart 2.—Absorption times of intracutaneous injections of solutions of dextrose and sodium chloride for patients with controlled diabetes.

times of the different solutions. For each test of four solutions the actual time of absorption was recorded under the appropriate vertical column and a line drawn to connect the four observations made at one

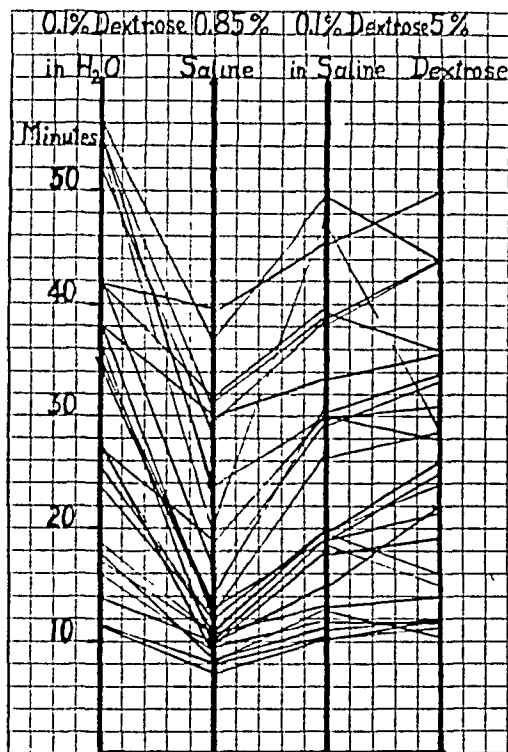


Chart 3.—Absorption times of intracutaneous injections of solutions of dextrose and sodium chloride for nondiabetic subjects.

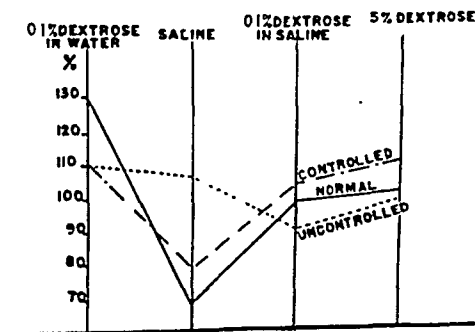


Chart 4.—Comparison of the absorption times of intracutaneous injections of solutions of dextrose and sodium chloride for persons with uncontrolled diabetes, persons with controlled diabetes and for nondiabetic subjects.

time. The lines connecting the vertical columns, therefore, indicate the values for a series of tests made at different times.

The total time for absorption of all solutions (table 1) was shortest for patients with uncontrolled diabetes and longest for normal subjects,

with patients with controlled diabetes occupying an intermediate position. Although the range of variation was rather broad for all three groups (charts 1, 2 and 3), the tendency for more of the series of readings to cluster around lower levels of absorption time was apparent for the patients with uncontrolled diabetes. It was observed (table 1) that for the last-named subjects absorption of the physiologic solution of sodium chloride and of 0.1 per cent solution of dextrose in water took the longest time (20.4 and 19.7 minutes respectively) and that of 5 per cent solution of dextrose and 0.1 per cent dextrose in physiologic saline solution required less time.

In chart 1 it may be observed that while in a number of tests the 0.1 per cent solution of dextrose in water was absorbed at a more rapid rate than was the physiologic solution of sodium chloride, in others the rate was the same or greater. The tendency for the lines to swing downward (shorter time) to the absorption level of 0.1 per cent dextrose

TABLE 1.—*Average Absorption Time*

Condition of Subject	0.1% Dextrose in Water	0.85% Solution Sodium Chloride	0.1% Dextrose in 0.85% Sodium Chloride	5% Dextrose in Water	Total Time, Minutes
Uncontrolled diabetes...	20.40	19.70	16.5	18.5	75
Controlled diabetes.....	22.5	16	21.5	22.4	82.4
No diabetes.....	35.3	18	26.0	27.3	106.6

in saline solution was clearly apparent. In case of the 5 per cent dextrose solution some of the lines swing down, some are parallel and others turn upward.

In the subjects with controlled diabetes the physiologic solution of sodium chloride required the shortest time for absorption, the 5 per cent and the 0.1 per cent solutions of dextrose in water the longest time and the 0.1 per cent of dextrose in physiologic solution of sodium chloride slightly less time. In chart 2 the altered status may be observed by the sharp swing downward of the greater number of the lines from the absorption level of 0.1 per cent solution of dextrose in water to that of physiologic solution of sodium chloride and then the definite upward swing (longer time) to the level of 0.1 per cent dextrose in physiologic solution of sodium chloride. Finally, most of the lines are either parallel or swing upward to reach the level for 5 per cent solution of dextrose, with some turning downward.

In the normal subjects (chart 3) the absorption tendencies of the solutions show the most defined pattern. Although among these subjects on the whole the solutions required a longer time for absorption than they did among patients with controlled diabetes, the close resemblance between the absorption patterns of the two types of subjects is apparent.

It was observed for patients whose diabetes was either under control or "out of control," as well as for the normal subjects, that considerable variations in the readings were obtained from time to time. In a small group which was observed daily for a week similar results were obtained. However, when the percentile ratio between the time of absorption of each solution and the average time for the series of solutions obtained on that day was taken, most of the differences between the series of readings taken on different days were eliminated. Therefore, while the rate of absorption of the various solutions varied markedly from day to day, the ratio of the time of absorption of each of the solutions to the average time for the series for that day remained fairly constant. To summarize the data obtained in terms of a percentile ratio between the average time of absorption for each of the solutions and the average time for the series for each of the three groups of subjects, chart 4 was

TABLE 2.—*Ratio of Rate of Absorption of Various Solutions to Rate of Absorption of Physiologic Solution of Sodium Chloride*

Condition of Subject	Solution			
	0.1% Dextrose in Water	0.85% Solution of Sodium Chloride	0.1% Dextrose in 0.85% Solution of Sodium Chloride	5% Dextrose
Uncontrolled diabetes.....	1.04	1.00	0.84	0.94
Controlled diabetes.....	1.41	1.00	1.34	1.40
No diabetes.....	1.99	1.00	1.47	1.54

drawn. It may be seen that the rate for the groups with controlled diabetes approaches that for the normal subjects.

Because comparison of absorption time of the saline solution with that of the various other solutions gave the most striking differences and because the saline solution represents an ionic solution and the others molecular solutions, all the other solutions employed were compared with it. It may be seen from table 2 that the ratio of the other solutions to the physiologic solution of sodium chloride tends to approach normal in the persons with controlled diabetes and differs more greatly in persons with uncontrolled diabetes. In the latter the values for the 0.1 per cent solution of dextrose in saline solution and for the 5 per cent solution of dextrose are less than those for the saline solution. In the persons with controlled diabetes the ratios for the 0.1 per cent solution of dextrose in water and the 5 per cent dextrose are definitely the highest, with the value for 0.1 per cent solution of dextrose in saline solution occupying an intermediate position. Among the normal subjects, the ratio for 0.1 per cent solution of dextrose in water is the

highest, with the 5 per cent solution of dextrose next and the 0.1 per cent solution of dextrose in saline solution the lowest.

A group of 10 diabetic patients was observed at frequent intervals from the time they were admitted with the diabetes out of control until the diabetes was brought under control. It was observed that it took from one to two weeks after the sugar levels of the blood and urine were brought down to normal before the absorption rates of the various solutions approached normal. The subjects with mild diabetes, the control of which was achieved and maintained by diet alone, showed the most prompt response in their absorption rates. The dextrose solutions were absorbed more rapidly than were solutions of sodium chloride before diabetic management was undertaken, while after the diabetes was brought under control the reverse was seen. On the other hand,

TABLE 3.—*Effect of Control of Diabetes on Rate of Absorption of Solutions of Dextrose and Sodium Chloride*

Condition of Subject	Solution			
	0.1% Dextrose in Water	0.85% Sodium Chloride	0.1% Dextrose in Sodium Chloride	5% Dextrose in Water
Absorption Time				
Uncontrolled diabetes.....	24.5	21.2	16.2	18.2
Controlled diabetes.....	22	15.4	22.4	24
Ratio of Absorption Time of Above Solutions to That of Physiologic Solution of Sodium Chloride				
Uncontrolled diabetes.....	1.15	1.00	0.76	0.86
Controlled diabetes.....	1.42	1.00	1.46	1.56

transient elevations in the level of sugar in the blood and urine were not reflected by changes in the absorption rates. The absorption rates for the same group of 10 patients, both with the diabetes out of control and with it under control, did not differ significantly from those for the larger groups of patients observed. The values obtained in the various stages of elevation of blood sugar and glycosuria were grouped together and contrasted with those obtained when the patients were sugar free and had more normal blood sugar values (table 3).

In 3 of the patients the typical changes in the ratio as the diabetes was brought under control were not observed. One patient had gangrene of the toes of one foot, the second moderately severe arteriosclerosis and the third severe diabetes.

It was found that in normal subjects (10 tests) urea was absorbed at about the same rate as a 0.1 per cent solution of dextrose in physiologic saline solution, that is, in 25 minutes as compared with 26 minutes and that the ratio of the absorption rate to that of the saline solution was 1.41 (compare with tables 1 and 2).



For the normal persons the average absorption rate for urea was distinctly greater than that for persons with diabetes. Among the latter the absorption rate was subject to wide fluctuations, and no consistent ratio was evident whether the basis for comparison was the rates for the two states of diabetic control or the rates for the other solutions, with the exception that in persons with controlled diabetes the solution of urea was usually absorbed more slowly than was the physiologic solution of sodium chloride.

#### COMMENT

In the diabetic patients as a group differences in the absorption rates of the different solutions depended on whether the diabetes was controlled or uncontrolled. The total absorption time of the solutions for the patients with uncontrolled diabetes was less than for those whose diabetes was controlled. This was probably due to a measure of dehydration which occurs in persons with uncontrolled diabetes. However, this was not the only factor. The 5 per cent solution of dextrose and the 0.1 per cent dextrose in saline solution were absorbed at a slightly faster rate than was the physiologic solution of sodium chloride, while the absorption rate for the 0.1 per cent solution of dextrose in water was almost the same as that for the last-named saline solution. On the other hand, among patients with controlled diabetes the dextrose solutions were absorbed at a definitely slower rate than was the saline solution.

In any subject repeated testing may reveal wide fluctuations in absorption time of the solutions; however, the relation of the absorption time of one solution to that of another at the time of testing revealed a far greater consistency than did the rate of absorption of each solution from test to test. For example, in a person with controlled diabetes if the saline solution was absorbed rapidly at one test, the other solutions were also absorbed at a relatively rapid rate; on the other hand, if in the same patient with the diabetes still under control the saline solution was absorbed at a slower rate, the other solutions were also absorbed at a relatively slower rate and the ratio between the solutions was not appreciably changed. The fluctuations from test to test for a given person may be due to daily variations in the state of hydration.

It was evident that differences in osmotic pressure and hydration could not explain adequately all of the changes observed. For persons with controlled diabetes the relation between the rates of absorption of various solutions was similar to that evident for normal subjects and differed from that for persons with uncontrolled diabetes. This difference may, to a certain extent, be explained by the assumption of differences in permeability.

The most consistent differences were obtained with the physiologic solution of sodium chloride, as compared with the isotonic solution of dextrose. The ratio between the two (dextrose/saline solutions) for the patients with uncontrolled diabetes was 0.94; for those with controlled diabetes it was 1.40, and for the normal subjects it was 1.54. The isotonic solution of urea gave results that were subject to wider fluctuations than those obtained with the other solutions, although among the normal subjects and the patients with controlled diabetes the absorption rates were as a rule slower than those noted with the saline solution, while the differences were definitely smaller than those between the isotonic solution of dextrose and the saline solution.

The results obtained with the 0.1 per cent solution of dextrose in water and the physiologic solution of sodium chloride confirm the findings of Seelig<sup>1</sup> with regard to the rate of absorption by persons with uncontrolled diabetes and by nondiabetic subjects.

#### SUMMARY

For 3 groups, persons with uncontrolled diabetes, persons with controlled diabetes and nondiabetic subjects, the absorption rates of intracutaneous injections of physiologic solution of sodium chloride, solutions of dextrose of various concentrations and a solution of urea were studied.

Definite differences were observed between the ratio of the absorption time of various solutions of dextrose to the absorption time of saline solution for persons with uncontrolled diabetes and the ratio for persons with controlled diabetes, throughout a relatively wide range of fluctuations in the actual absorption times.

The ratio of the absorption time of the various solutions of dextrose to that of the saline solution for the persons with controlled diabetes was similar to the ratio for the normal subjects but differed from that for the persons with uncontrolled diabetes.

# PROLONGED SURVIVAL AFTER PERFORATION OF THE INFARCTED INTERVENTRICULAR SEPTUM IN CORONARY ARTERIAL DISEASE

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In 1934 Sager<sup>1</sup> reviewed the literature on perforation of the infarcted interventricular septum in coronary thrombosis and reported a case of his own in which the diagnosis was made ante mortem. The reader is referred to his paper for an excellent summary of all previously reported cases of this condition and for criteria for its diagnosis during life. In most cases the occurrence of septal perforation in the course of coronary occlusion is signalized by the sudden appearance of a forceful thrill and murmur shortly after infarction. As in congenital septal defect, the smaller the aperture the louder the murmur. Larger septal defects may be associated with a diastolic murmur as well.

Although in all the cases reviewed by Sager the patients died within ten days after the occurrence of perforation, he predicted that an occasional instance of recovery might be found in which the infarct had undergone repair with scar tissue and in which perforation had persisted. Since then Huber<sup>2</sup> has reported the case of a patient surviving sixteen days in whose heart organization of the edges of the defect had already begun. A patient whose case Mahrburg<sup>3</sup> reported lived four weeks, and at autopsy a fibrous bulge containing four small defects was found in the septum. Gross and Schwartz<sup>4</sup> described a circular septal defect, several centimeters in diameter, occurring in a patient who died fourteen months after the onset of chronic cardiac failure. In the case reported by Stanley<sup>5</sup> the diagnosis was made clinically, and the patient eventually died of heart failure with hemiplegia five months after the onset.

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1. Sager, R. V.: Coronary Thrombosis: Perforation of the Infarcted Interventricular Septum, *Arch. Int. Med.* **53**:140 (Jan.) 1934.

2. Huber, H.: Ueber erworbene Defekte der Herzkammerscheidewand, *Ztschr. f. Kreislaufforsch.* **27**:825, 1935.

3. Mahrburg, S.: Durchlöcherung der Herzkammerscheidewand mit chronischem Verlauf, Frankfurt. *Ztschr. f. Path.* **47**:552, 1935.

4. Gross, H., and Schwartz, S. P.: A Case of Acquired Interventricular Septal Defect Associated with Long-Standing Congestive Heart Failure, *Am. Heart J.* **11**:626, 1936.

5. Stanley, D. F.: Acquired Interventricular Septum Defect: Report of a Case, *Am. Heart J.* **14**:240, 1937.

## REPORT OF A CASE

*History.*—C. H., a chemical operator 57 years old, was admitted to St. Peter's Hospital Jan. 11, 1939. He had been well until one month before admission, when he had an attack of severe precordial pain which lasted throughout the night. After that he had constant dull pain in both loins and a severe dry cough. Two weeks after the onset he became short of breath on slight exertion and began to have pain in the right upper quadrant of the abdomen.

*Physical Examination.*—The patient was well developed and well nourished. He appeared weak, dyspneic, pallid and slightly cyanotic. The veins of his neck were distended and pulsating, and he was unable to lie flat. The heart was greatly enlarged to the left and downward. The heart sounds were poor, and a loud systolic murmur and a diastolic murmur were heard over the apex. A palpable thrill was also felt over the apex. These murmurs were not transmitted to the base. The second aortic sound was faint, and the second pulmonic sound was accentuated. The pulse rate was 94 beats per minute; the pulse was weak,



Fig. 1.—Electrocardiogram taken one month after the onset of symptoms.

and the rhythm was irregular as a result of frequent premature beats. The blood pressure was 118 systolic and 70 diastolic. Moist rales were heard at the base of the left lung posteriorly, and signs of pleural effusion were noted at the base of the right lung. The liver was markedly enlarged and tender. No edema or ascites was detected.

*Laboratory Examination.*—Examination of the blood yielded the following information: hemoglobin concentration, (Sahli) 81 per cent; red cells, 4,200,000 per cubic millimeter; white cells, 5,800 per cubic millimeter, with 66 per cent polymorphonuclear leukocytes; Wassermann reaction, negative; urea nitrogen, 8.5 mg. per hundred cubic centimeters, and sugar, 85 mg. per hundred cubic centimeters. The urine was acid and had a specific gravity of 1.028; albumin was present in a moderate trace, but there was no sugar or acetone. Microscopically, a few white cells were seen. Roentgenologic examination of the chest revealed a markedly enlarged heart of aortic type and a pleural effusion on the right side.

*Electrocardiogram.*—The electrocardiogram (fig. 1) showed a regular sinus rhythm interrupted by many ventricular premature beats. The rate was about 75 beats per minute. The P waves were wide and notched, of the type associated

with auricular enlargement. The auriculoventricular conduction time, i. e., the PR interval, measured about two-tenths second, the upper limit of normal. The QRS complexes were wide, notched and slurred, with left axis deviation, and the RST transitions in leads I and II were slightly elevated.

*Clinical Diagnosis.*—The sudden onset of symptoms followed by rapid cardiac decompensation suggested coronary arterial occlusion. The wide, notched and slurred QRS complexes in the electrocardiogram indicated intraventricular block, as is seen in cases of damage to the septum, and the elevation of the RS-T segment indicated recent myocardial damage.<sup>6</sup> The large heart of aortic type, the loud systolic murmur, the precordial thrill, the faint second aortic sound and the slightly low blood pressure also suggested the presence of aortic stenosis as a cause of the failure of both ventricles. The possibility of ventricular septal defect was not considered.

*Course.*—The patient lived twelve weeks after admission to the hospital. In the course of this time the evidences of failure of the right side of the heart increased, despite treatment with digitalis and mercurial diuretics. Sacral and scrotal edema appeared, and repeated thoracentesis was required because of the rapid reaccumulation of fluid in the right pleural cavity. A roentgenologic examination of the chest after withdrawal of fluid revealed shrinkage and dense consolidation of the lower third of the right lung. The venous pressure measured by the direct method was 23.5 cm., rising to over 26 cm. on pressure over the right upper quadrant. The swelling of the liver became enormous, and slight icterus appeared. On March 3 moderate renal impairment was indicated by the rise of urea nitrogen to 27.3 mg. per hundred cubic centimeters of blood and by the excretion of only 12 per cent of injected phenolsulfonphthalein in two hours. In view of the normal concentrating ability of the kidney, these findings were attributed to chronic passive congestion of the kidneys. The intractable tendency to edema and effusion was attributed to the combination of heart failure, renal insufficiency and hypoproteinemia, the last being ascribed to undernutrition and possibly hepatic insufficiency. The proteins of the plasma were found to be 4.6 Gm. per hundred cubic centimeters, with a globulin deficiency (albumin 3.5 Gm., globulin 1.1 Gm.). The patient's temperature remained normal throughout most of his stay in the hospital; in the first two weeks his cardiac rate ranged between 40 and 48 and thereafter between 72 and 82 per minute. His blood pressure did not change significantly. Despite his poor condition, the harsh systolic murmur at the apex was distinct at all times and the pulmonic second sound remained accentuated. He died on April 12, 1939, approximately four months after the onset of his cardiac symptoms.

*Postmortem Examination.*—The anatomic diagnoses were as follows: coronary atherosclerosis, with complete occlusion of the left anterior descending branch and moderate narrowing of the right coronary artery; healed myomalacia, with extensive fibrosis of the left ventricle and the interventricular septum; large aneurysm of the left ventricle; double perforation of the interventricular septum in the area of previous infarction; localized endocardial sclerosis of the right ventricle opposite the perforation; localized pericardial adhesion; hypertrophy and dilatation of the right ventricle; anasarca, with enormous right hydrothorax; complete compression atelectasis of the entire right lung, with chronic serofibrinous pleuritis; compensatory emphysema of the left lung; chronic passive congestion of the liver (marked), spleen, kidneys, gastrointestinal tract and lungs; slight icterus; acute gastric dilatation, and anemic infarction of the right kidney.

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6. The electrocardiogram reported here was interpreted by Dr. Arthur Master.

*Examination of the Heart.*—The heart weighed about 400 Gm. The pericardial surfaces were smooth, except for an area of dense fibrous adhesion about 4 cm. wide overlying the anterior interventricular groove in its middle portion. The anterior wall of the left ventricle beneath this point was extremely thin and flabby and was stretched into an aneurysmal pocket. When the left ventricle was opened (fig. 2) the aneurysm was seen to be much larger than was apparent externally. Its size approximated that of a small orange. It was formed in part by the anterior wall of the left ventricle and in part by the adjacent interventricular septum. Its inner surface was composed of tough, gristly, pearly white fibrous tissue overlaid by an area of adherent mural thrombus. The latter, which was grayish red, projected considerably into the lumen of the aneurysm and measured about 4 cm. in width. The greatest thickness of the wall of the aneurysm was less than 5 mm. It involved about five sixths of the interventricular septum

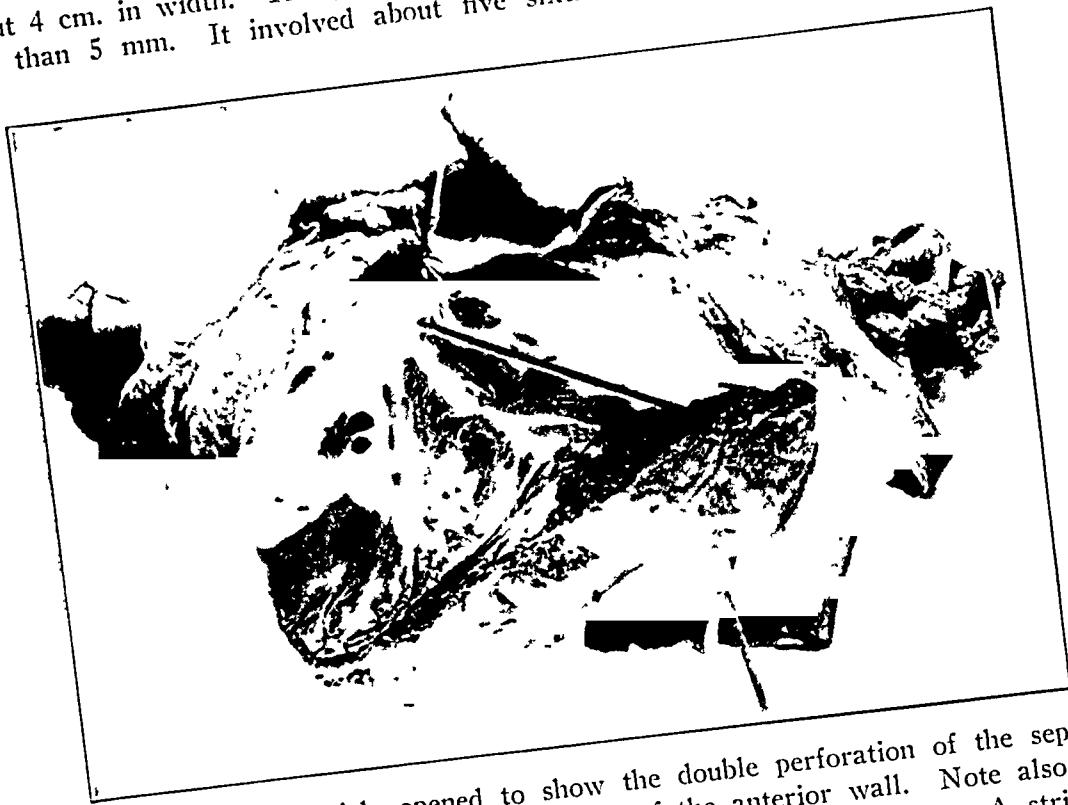


Fig. 2.—Left ventricle opened to show the double perforation of the septum and the aneurysmal dilatation and thinning of the anterior wall. Note also the wide scarring of the septum, overlaid in part by a mural thrombus. A strip of adherent pericardium is visible on the anterior surface of the ventricular aneurysm.

and was thinnest at its upper mesial border, where the muscle substance was replaced by white scar tissue 1 mm. thick. Here two ovoid perforations were seen, separated by a bridge of firm scar tissue 2 mm. wide. The lower perforation was 4 mm., the upper 5 mm., in greatest diameter. Their circumferences were thin and perfectly smooth and did not yield to stretching. In addition to the aneurysm, the left ventricle presented considerable dilatation and some hypertrophy, especially in its posterolateral portion and in the anterior papillary muscle. Section of the myocardium showed patchy fibrosis.

The right ventricle was considerably dilated and hypertrophied. The right ventricular surface of the septum presented only a moderate bulge, which was most pronounced in the region of the perforations where the septum had become

entirely replaced by scar tissue. The latter formed an irregular, pearly white streak extending a few centimeters above and below the perforations (fig. 3). The remainder of the right ventricular endocardium was of usual appearance, except for a well defined round patch of whitish endocardial thickening on the anterior wall. This area measured about 2 cm. in width and was situated in the outflow tract of the right ventricle immediately opposite the septal perforation. On section the sclerosis was found to be confined to the endocardial layer. The anterior descending branch of the left coronary artery was markedly narrowed by calcified atheroma beginning 0.5 cm. below its origin, and in several places it was totally occluded. A small bulging plaque of soft atheroma in the intima of the right coronary artery about 3 cm. from its origin caused moderate narrowing of its lumen. The remaining coronary arterial branches showed some atheroma but no significant narrowing. The coronary ostiums were patent. The endocardium of the valves was free of significant change.



Fig. 3.—Interior of the right ventricle showing septal perforations. Note the hypertrophy of the wall of the right ventricle opposite the septum and the circumscribed area of white endocardial sclerosis (incised post mortem).

*Lungs.*—The right pleural cavity contained about 2,500 cc. of yellowish, slightly turbid fluid. The right lung was completely collapsed in a uniform manner which preserved its shape but reduced it to about one-third its normal size. It was peculiarly firm and rubbery, and its surface was thinly overlaid with fibrinous exudate, which had a reticulated appearance. On section the lung tissue appeared completely airless and totally consolidated. The bronchi were correspondingly narrowed. The left lung was somewhat emphysematous, and on section appeared congested and mottled, with a few small areas of slight pneumonic infiltration. In contrast to the right lung, the left lung cut with great ease. The tracheobronchial nodes were small and anthracotic.

Microscopically, sections of the right lung showed marked alveolar atelectasis and compression of bronchioles. The capillaries were dilated and tortuous, and the alveolar epithelium was swollen and desquamated. The veins were distended with blood, and the interlobular and peribronchial septums and subpleural connective tissue were edematous and moderately infiltrated with leukocytes, chiefly

mononuclear in type. The arteries and arterioles were slightly narrowed by fibrous intimal hyperplasia and medial hypertrophy. Dense masses of hyalinized fibrin were deposited on the outer layer of the pleura. Sections of the left lung showed mild uniform hyperinflation of the alveoli and marked capillary congestion, with recent patchy hemorrhage. Veins were distended with blood, and slight fibrous thickening was apparent in the media. Patchy slight fibrinopurulent exudate was present in the alveoli.

#### COMMENT

The congenital variety of uncomplicated defect of the interventricular septum is of little clinical significance in most cases. Acquired septal defect is probably always of serious import, depending on the nature of the underlying disease (septal infarction, septal ulceration<sup>7</sup>) and on the sudden imposition of unusual strain late in life on an aging right ventricle. In most cases of septal defect which results from coronary closure death occurs within the first few days from the acute heart failure and circulatory shock of extensive myocardial infarction. In the rare case of survival beyond the critical phase of infarction death is almost inevitable within a few months as a result of right ventricular failure. Although only 3 other cases are on record in which the patient lived one month or longer after septal rupture, congestive heart failure was pronounced in all of them, as well as in the case just described. One is impressed in these cases with the unyielding character of the right ventricular failure that occurred in spite of persistent efforts at treatment. On the other hand, left ventricular failure was not marked, and, as is often noted in cases of other types of heart failure, it was mitigated to a great extent by the insufficiency of the right ventricle.<sup>8</sup>

The mechanism of heart failure in these 4 cases of septal perforation can be explained in terms of at least three components: the leak from the left to the right ventricle, the fibrous replacement of the septal myocardium and the permanent injury to part of the left ventricle. Apparently the burden in these cases was borne chiefly by the right ventricle. Clinically anasarca and hepatic engorgement were the dominant features; the pulmonic second sound was greatly accentuated in 2 cases in which it was mentioned, and autopsy disclosed considerable hypertrophy and dilatation of the right ventricle. In the case herein reported the venous pressure was recorded as 23.5 cm. (direct method), and at autopsy a telltale plaque<sup>1</sup> of endocardial sclerosis opposite the septal fistula indicated the force with which the jet of blood from the left ventricle struck the opposite wall of the right ventricle.<sup>7</sup> The small area and uniform appearance of this plaque are of interest as proof of the

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7. Saphir, O.: *Anatomic Evidence of Functional Disorders of the Heart*, Arch. Path. **16**:315 (Sept.) 1933.

8. Fishberg, A. M.: *Heart Failure*, ed. 2, Philadelphia, Lea & Febiger, 1940, p. 449.



constancy of direction of the jet and as a minor confirmation of Moschcowitz' thesis that vascular sclerosis is determined by intravascular tension.<sup>9</sup>

Right ventricular failure subsequent to coronary occlusion is not to be regarded, however, as necessarily indicative of septal perforation. In the majority of cases it is the result of failure on the left side and is commonly explained by backward pressure through the pulmonary circulation, by recurrent pulmonary emboli and by other factors. Among the last should be mentioned the excessive intrusion within the right ventricular cavity of the bulging convexity of the interventricular septum associated with marked concentric hypertrophy of the left ventricle (Bernheim syndrome).<sup>10</sup> Another cause of septal bulging, *myomalacia with replacement fibrosis*, was seen in the case reported here, in which most of the septum and part of the anterior wall of the left ventricle formed a large aneurysmal sac.

In many instances of coronary disease with right-sided failure the aforementioned mechanisms seem inadequate to explain the degree of failure. The relative immunity of the right ventricle to coronary infarction adds to the difficulty of explanation. Perhaps this difficulty is the result of the current tendency to make sharp distinctions between left ventricular and right ventricular function, as exemplified in special forms of heart failure. While such distinctions are of great clinical usefulness, they tend to perpetuate the old concept of two simultaneously but independently acting ventricles. The important anatomic studies of MacCallum,<sup>11</sup> Mall,<sup>12</sup> the Robbs<sup>13</sup> and others have opened new avenues of research into the physiology of the ventricular musculature. Of six well defined muscle tracts of the ventricles, only one, the deep bulbospiral muscle, lies wholly within the left ventricle; the other five muscles contribute through their origins and insertions to the formation of both ventricles. The superficial sinospiral and the superficial bulbospiral muscle arise from the right and the left atrioventricular rings, respectively, and wind downward and across the anterior and the posterior

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9. Moschcowitz, E.: The Cause of Arteriosclerosis, *Am. J. M. Sc.* **178**:244, 1929.

10. Fishberg,<sup>8</sup> p. 447.

11. MacCallum, J. B.: On the Muscular Architecture and Growth of the Ventricles of the Heart, in *Contributions to the Science of Medicine, Dedicated by His Pupils to William Henry Welch on the Twenty-Fifth Anniversary of His Doctorate*, Baltimore, Johns Hopkins Press, 1900, p. 307.

12. Mall, cited by Robb and Robb.<sup>13c</sup>

13. (a) Robb, J. S.; Hiss, F., and Robb, R. C.: Localization of Cardiac Infarcts According to Component Ventricular Muscles, *Am. Heart J.* **10**:287, 1933. (b) Robb, J. S.: The Structure of the Mammalian Ventricle, *M. Woman's J.* **41**:65, 1934. (c) Robb, J. S., and Robb, R. C.: Abnormal Distribution of the Superficial Muscle Bundles in the Human Heart, *Am. Heart J.* **15**:597, 1938.

interventricular groove toward the apex, where they penetrate deeply to form the papillary muscles of the mitral valve. The deep sinospiral muscle, which arises from nearly the entire circumference of the left atrioventricular ring, curves downward over the lateral and posterior wall of the left ventricle, where it forms the rounded, fleshy lower border (*margo obtusus*), and splits at the posterior interventricular groove to enclose the cavity of the right ventricle, comprising 75 per cent of its substance normally. The scroll muscle arises deep within the base of the right ventricle, completely encircles its upper portion in a clockwise course and thence passes forward through the septum to reach the superficial layers of the left ventricle anteriorly, where it fuses with the fibers of the superficial muscles. The longitudinal interventricular muscle arises from both atrioventricular rings and the aortic septum and courses forward and downward through the septum to emerge anteriorly, where it fuses with the superficial sinospiral muscle above the apex. From the foregoing descriptions it is apparent that the superficial sinospiral and the superficial bulbospiral muscle encircle both ventricles externally and that the deep sinospiral muscle and the scroll muscle encircle both ventricles more deeply. The septum is contributed to by the deep sinospiral muscle, the scroll muscle and the longitudinal interventricular muscle. Experimental injury of selected muscle tracts produces serious functional impairment of the ventricles in the case of the deep muscles and relatively insignificant impairment in the case of the superficial muscles.<sup>13a</sup>

It remains for future workers to determine the extent to which these separate muscle tracts act as functional units. Can necrosis through infarction of an individual muscle at one point of its course cause serious disruption of its function as an entire unit? Certain intimations of this possibility are observed clinically, for instance in those cases of predominant right ventricular failure that results from extensive infarction of the left ventricle not including the septum in which the degree of pulmonary congestion is not especially outstanding. Such cases, for want of a better explanation, have been considered by some as examples of "forward failure." As an alternative hypothesis, the suggestion is offered that in such cases a remote injury, e. g., one in the left ventricle, may communicate its effects to the right ventricle through individual muscle tracts which are continuous in both ventricles. The greatest threat to normal function of the right ventricle has been shown to lie in injury to the deep sinospiral muscle, which contributes about three fourths of the muscle substance of the right ventricle. This muscle, moreover, is vulnerable to injury over a large area within the lateral and posterior wall of the left ventricle before it enters into the formation of the right ventricle and is often involved in infarction of the posterior and lateral wall of the left ventricle. In cases of infarction of the septum

a number of important fiber tracts may be caught in a relatively small area of injury, with the result that either the left or the right or both ventricles may suffer. On the other hand, according to the same hypothesis, the septum itself may suffer as a result of infarction of one of its constituent muscles at some point within the left ventricle.

It is rather surprising that the role of the interventricular septum in cardiovascular dynamics has not been stressed to the degree that it deserves. The case recorded here, in which right-sided failure was outstanding, focuses attention on the septum as a truly important element in this problem. The functions which are peculiar to the septum are not easily understood, unless by analogy. The anatomic justification for ascribing an active and independent function to the septum is found in the existence of such muscles as the scroll muscle and the longitudinal interventricular muscle, previously described. In both these the fibers are directed in a way to suggest that their chief activity consists in shortening the septum along each major axis during systole. Its effect is probably both to aid in the systolic contraction of the heart as a whole and to preserve the normal differential in intracardiac pressures of the left and the right ventricle during systole and diastole. Septal failure through myofibrosis or perforation permits the heart to revert to a condition approaching that of the *cor triloculare*, in which blood is propelled by a common ventricle. In that case the burden is transferred to those layers of the heart muscle which are common to both ventricles. The task of maintaining the systolic and diastolic tension in the systemic arteries must then be shared in unusually great part by the right ventricle. When this extra burden proves beyond its powers compensation is largely, if not entirely, manifested as right-sided failure.

#### SUMMARY

Rupture of the left ventricle after infarction is immediately fatal unless the area of softening is situated in the interventricular septum. In the latter case death may be delayed several days, and then occur as a result primarily of the severe shock and heart failure resulting from coronary occlusion. Prolonged survival is rare and is characterized by intractable right ventricular failure and the presence of the harsh systolic murmur of interventricular septal defect.

The interventricular septum considered as a functional entity is of particular significance, both as a component of deep muscle tracts common to both ventricles and as an agency for protecting the right ventricle by preserving the differential in pressure between the two ventricles.

# PRIMARY PORTAL PHLEBOSCLEROSIS

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Although phleboscrosis of the portal system is recognized as a primary entity, its definition is obscure and its pathogenesis and etiology require further investigation. Since its occurrence has been adequately established,<sup>1</sup> it should be more carefully sought for at autopsy. It is the purpose of this paper to indicate how it may be clinically identified more frequently. It is also proposed to employ henceforth the name "primary portal phleboscrosis" for clarification and uniformity.

Up to 1928,<sup>2</sup> 29 cases were reported in children, but few in adults. The exact number is difficult to ascertain in view of the existing confusion. In many of these cases the condition appeared to resemble Banti's syndrome, as it did in my case. However, on further study or at autopsy, the question of some primary obstruction of the portal circulation, with or without coexisting thrombosis or sclerosis of either the splenic or the portal vein or of both, arises. Wilson and Lederer<sup>2</sup> presented the case of a boy aged 16 months. Haenelt<sup>3</sup> added another case and mentioned 8 cases in the literature in which the condition was designated as Banti's syndrome but at autopsy proved to be either portal

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From the service of Dr. C. H. Greene, Kings County Hospital, and the Long Island College of Medicine Division, J. Hamilton Crawford, Director.

1. (a) Spiegelberg, H.: Verkalkung der Wandungen der thrombotischen Pfortader, Virchows Arch. f. path. Anat. **142**:547, 1895. (b) Borrmann: Beiträge zur Thrombose der Pfortaderstammes, Deutsches Arch. f. klin. Med. **59**:283, 1897. (c) Welch, W. H.: Thrombosis, in Allbutt, T. C.: System of Medicine, New York, Macmillan & Company, 1899, vol. 7, p. 155. (d) Buday, K.: Ueber die Sklerose der Pfortader, Centralbl. f. allg. Path. u. path. Anat. **5**:161, 1903. (e) Hart, C.: Ueber die kavernöse Umwandlung der Pfortader, Berl. klin. Wchnschr. **50**:2231, 1913. (f) Winkler, H.: Ueber primäre Pfortaderthrombose bei Pfortadersklerose und bei chronischen Milztumor, Ztschr. f. Path. **17**:377, 1915. (g) Gruber, G. B.: Beiträge zur Pathologie der dauernden Pfortaderverstopfung, Deutsches Arch. f. klin. Med. **122**:319, 1917.

2. Wilson, S. J., and Lederer, M.: Splenomegaly Portal Phleboscrosis, Am. J. Dis. Child. **38**:1231 (Dec.) 1929.

3. Haenelt, M.: Beitrag zur Frage der Sklerose im Pfortadergebiet, Med. Klin. **24**:622 (April 20) 1928.

or splenic phlebosclerosis, as described microscopically by Brüning and Schwalbe.<sup>4</sup>

The exact point of obstruction may occur anywhere in the portal system. In the case reported by Wilson and Lederer<sup>2</sup> the constriction occurred in the proximal portion of the portal vein. Galloway<sup>5</sup> found the point of obstruction at the junction of the splenic and the mesenteric vein. In my case, both the portal vein and its splenic branch were involved.

#### REPORT OF A CASE

R. L., an Italian woman aged 21, entered Kings County Hospital with a history of gastric hemorrhage, with loss of 1 quart (946 cc.) of blood, seven years before, at the age of 14. The following year she had had three hematemeses in twenty-four hours but no other complaints. A diagnosis of Banti's disease was made, and splenectomy was performed at that time. However, hemorrhages persisted and were severe, amounting to several pints each time. A similar attack was the occasion for her entrance to the hospital. Weakness was rapidly progressive. Prior to the onset seven years before she had been in good health. She had suffered from influenza seven years previously, scarlatina and diphtheria at the age of 1 year, but had had no trauma, infections or operations. She seldom smoked, occasionally took alcohol and was a moderate coffee drinker. The father had died at the age of 22 of pneumonia, and the mother had disappeared.

The patient was well developed and well nourished and appeared acutely ill. There was evidence of air hunger. The edge of the liver was firm and palpable at the costal margin. There was no fluid or mass.

Laboratory studies revealed severe secondary anemia, with normal white cell and differential counts. The results of urinalysis were essentially normal. The blood contained 100 mg. of sugar, 1.6 mg. of creatinine, 75 mg. of urea, 3.7 mg. of albumin and 2.0 mg. of globulin per hundred cubic centimeters; the albumin-globulin ratio was 1.8; the spinal fluid was normal, and the Wassermann reaction of the blood was negative. Findings seven years previously had revealed normal erythrocyte fragility, a negative Widal reaction, sterile blood cultures, severe secondary anemia, an icteric index of 4.5 and normal roentgenograms of the gastrointestinal tract and the chest.

A diagnosis of Banti's disease, with rupture of an esophageal varix, was made. About two and one-half weeks after admission the patient had another hemorrhage. She went into shock and was given a transfusion, with rapid improvement. The following day an operation was performed. Two large veins on the diaphragm, crossing toward the esophagus and nearly 0.5 cm. in diameter, were ligated. Two cubic centimeters of sodium morrhuate was injected into a large vein on the lesser curvature of the stomach. After the operation a temperature of 103 F. developed. The patient's course of illness was rapidly downhill, and she died three days after the operation.

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4. Brüning, H., and Schwalbe, E.: *Handbuch der allgemeinen Pathologie und der pathologischen Anatomie des Kindesalters*, Munich. J. F. Bergmann, 1924, vol. 2, p. 1225.

5. Galloway, J.: Splenomegaly with Anemia and Hemorrhages, *Brit. J. Child. Dis.* 13:64, 1916.

The spleen, removed at the Metropolitan Hospital seven years previously, weighed 493 Gm. It was reported to have been enlarged, congested and firm. The edge of the cut section was sharp and flat, and the pulp was purplish red. The splenic vessels were enlarged. Microscopically, there was marked peri-vasculitis of fibrous type, with hyperplasia of the trabeculae. The germinal centers appeared large in some places and small in others. The parenchyma was congested, but no blood pigment was present. No note was made concerning the appearance of the portal vein. A diagnosis of Banti's disease was made.

On postmortem examination, the portal vein was of uniform caliber but its internal diameter was only about half the normal, measuring 0.5 cm. It was almost completely occluded by an adherent gray thrombus, which left only an eighth of the lumen patent. The superior mesenteric vein was also markedly narrowed and presented the same appearance as the portal vein. Most of the tributaries of the superior mesenteric vein to the small and the large bowel were occluded by adherent gray thrombi. The superior and inferior hemorrhoidal veins were dilated and slightly varicose but not thrombosed. Many of the veins about the cardiac end of the stomach were prominent, varicose and thrombosed. The paraumbilical vein was represented by a fibrous strand. There was no caput medusae. The thoracoepigastric vein was not prominent superficially; the azygos vein was moderately dilated, and there were many varicose veins in the lower half of the esophagus, but no point of rupture was found. The left common iliac vein was completely occluded by a gray adherent thrombus, the center of which was loose and necrotic. This could be traced distally into the external iliac and femoral veins, and it extended for about 1 inch (2.5 cm.) into the proximal portion of the hypogastric vein. The inferior vena cava was smooth throughout and free of thrombi. The right common iliac vein was patent and the intima was smooth. On the upper left side the great omentum and its vessels were adherent to the parietal peritoneum covering the lateral abdominal wall. The splenic artery was markedly narrowed, and there were a few small sclerotic plaques in its intima. The coronary arteries and aorta were normal. The branches of the pulmonary artery in the lower lobe of the right lung were filled with loosely adherent, gray, soft thrombi, with the production of multiple hemorrhagic infarctions. The blood vessels of the cardiac portion of the stomach were prominent. In the jejunum there was an area of venous infarction 2 inches (5 cm.) in length which was softened and friable.

Microscopically (figs. 1, 2 and 3) the liver showed marked fatty changes replacing the liver cells, the lobular architecture being fairly well preserved. There were round cell infiltrations around proliferated bile ducts and portal canals, as well as moderate reduplication of the small bile ducts. There was also chronic adhesive perihepatitis. The portal vein was filled with early organizing thrombi, and the wall showed evidence of marked thickening due to increased fibrous connective tissue in all layers. The smooth muscle was replaced by irregularly hyalinized areas of connective tissue. There was no evidence of atheromatous change or calcification. There were marked fibrous tissue proliferation and diffuse round cell infiltration surrounding the thrombi. The internal elastic membrane was frayed, thickened and interrupted. The final anatomic diagnosis was primary phleboscrosis of the superior mesenteric and splenic veins; multiple thromboses of the portal, superior mesenteric, left common iliac, external iliac, femoral, hypogastric and pulmonary veins, the submucosal veins of the stomach and the small intestine and the veins of the lymph nodes, and secondary anemia.

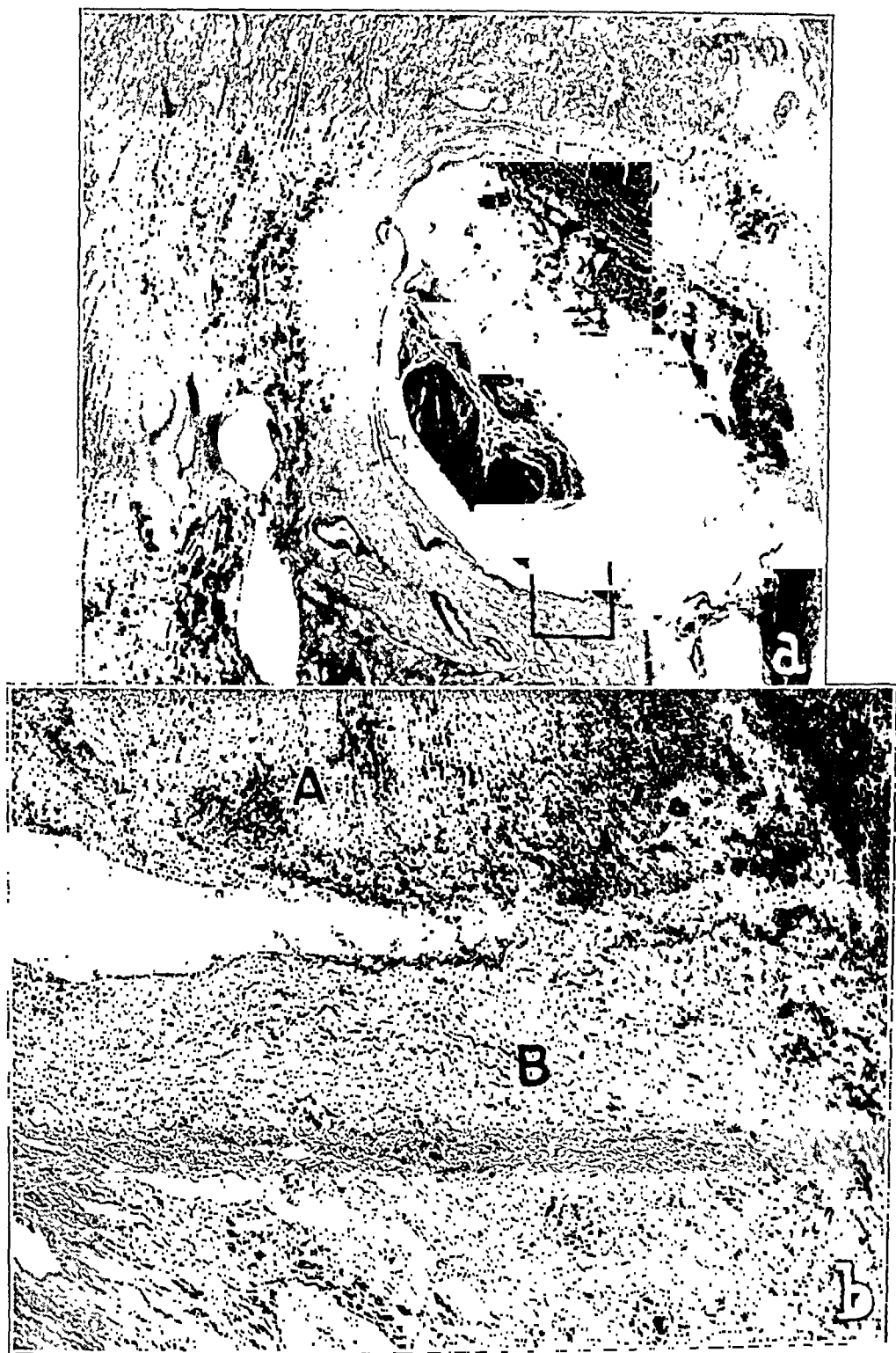


Fig. 1.—(a) A thickened vein and an attached thrombus ( $\times$  about 10). (b) A greater magnification ( $\times$  about 70) of the tissue in (a) indicated by square, the thrombus (A) at the point of attachment and the wall of the vein (B). The venous wall shows evidence of marked thickening due to fibrous connective tissue and hyalinization. The smooth muscle is replaced by irregular hyalinized areas of connective tissue. There is no evidence of calcification.

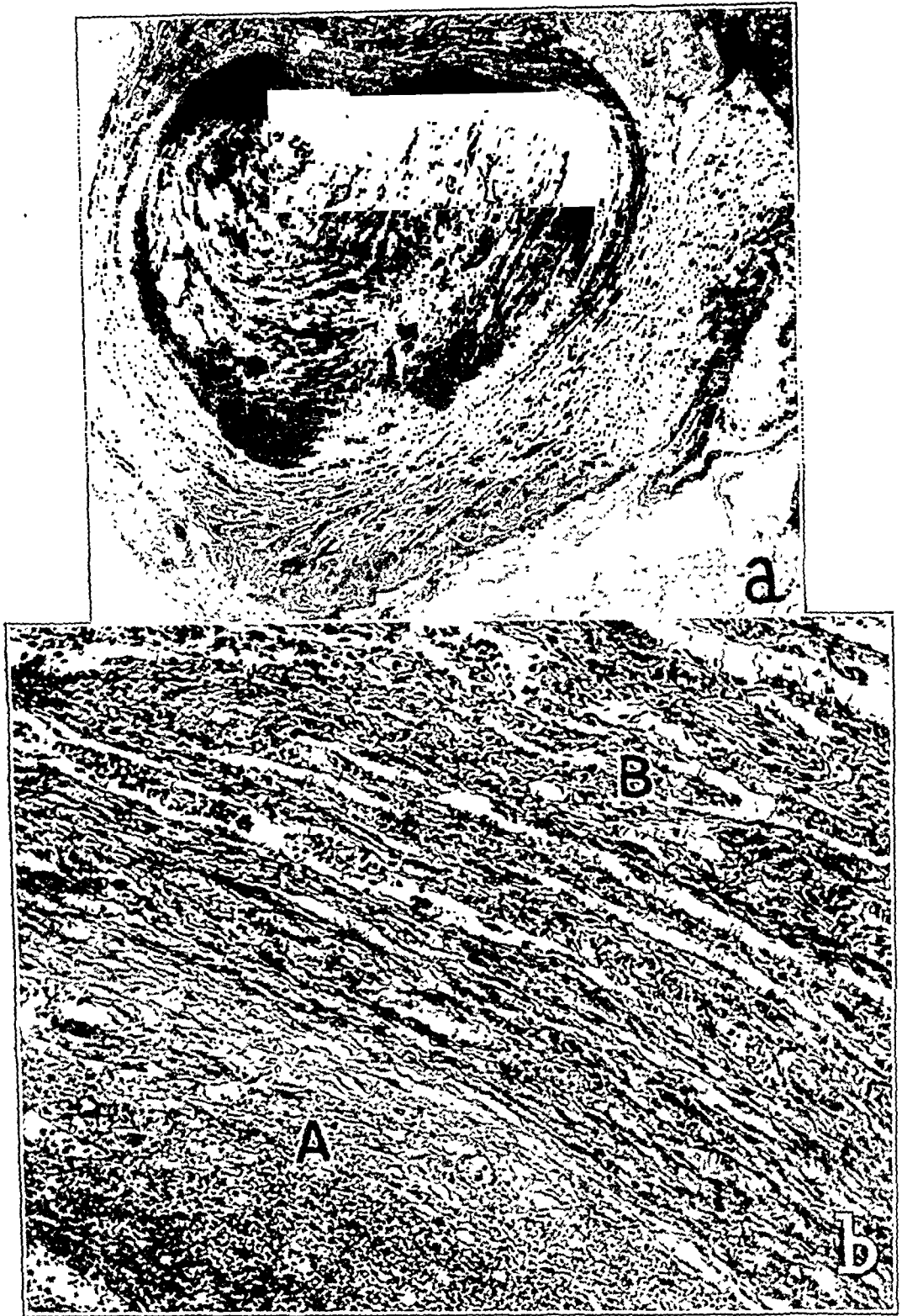


Fig. 2.—(a) Complete occlusion of the portal vein by an organizing thrombus ( $\times$  about 10). (b) The attached thrombus (A) and the wall of the vein (B) more highly magnified ( $\times$  about 142), showing the marked proliferation of fibrous tissue and the diffuse round cell infiltration surrounding it. The elastica is frayed, thickened and interrupted.



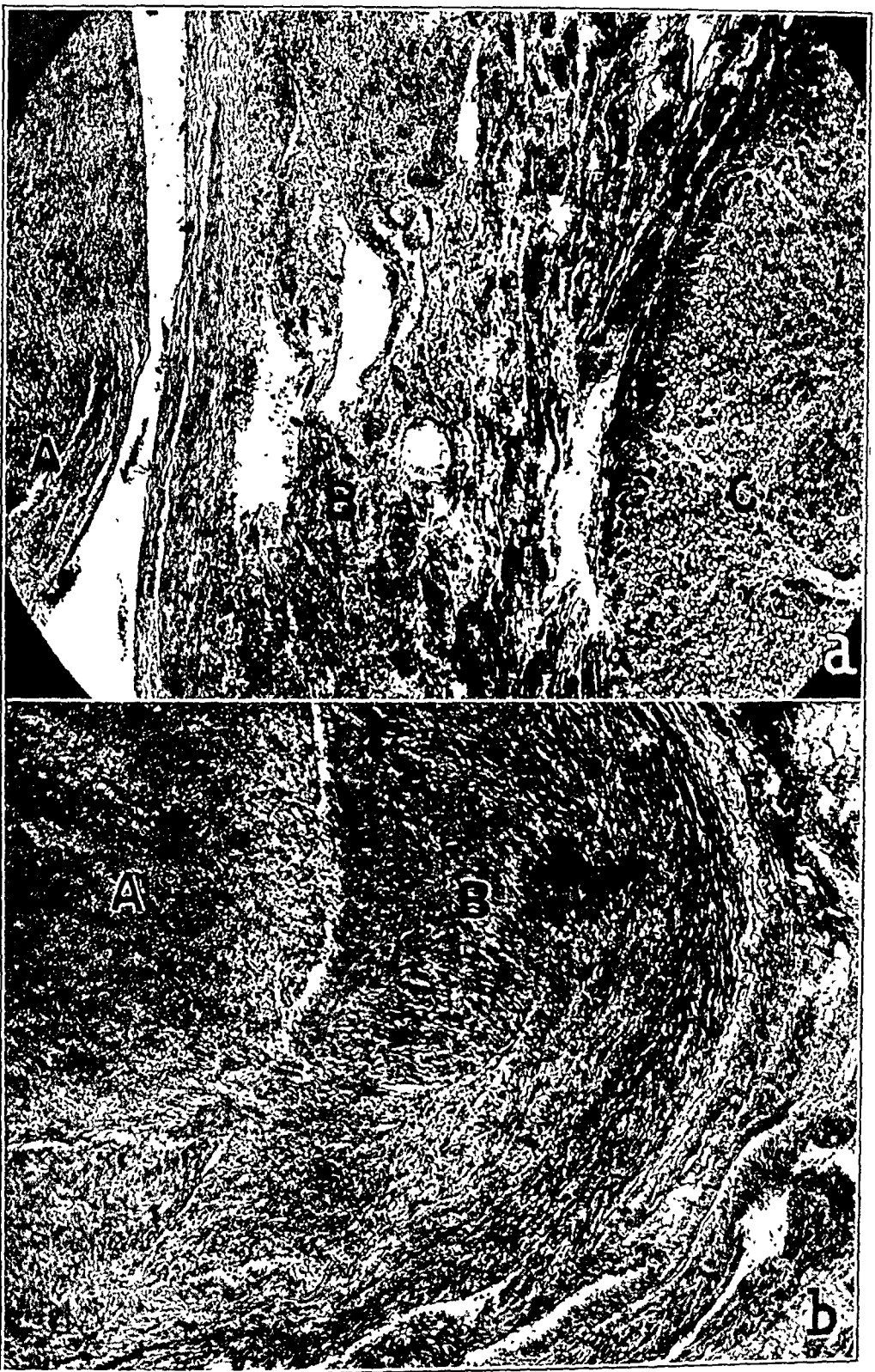


Fig. 3.—(a) An occluding thrombus (*A*) of the portal vein, with partial organization and disintegration. Also visible are the typical necrotic changes (*B*) and marked fatty changes of the hepatic cells (*C*), although the lobular architecture is well preserved. There is marked proliferation of the bile duct, with reduplication and round cell accumulations ( $\times$  about 55). (b) A large organizing thrombus (*A*) adherent to the wall of the superior mesenteric vein (*B*). The latter shows the usual fibrotic thickening ( $\times$  about 68).

## PATHOLOGY

It has long been argued that the extreme splenomegaly of Banti's syndrome is due to primary obstructive lesions of the portal and splenic veins.<sup>6</sup> Nevertheless, the fact that the spleen in cases of cardiac decompensation never shows such extreme enlargement is somewhat against this view. Menon<sup>7</sup> by experimental operation produced the same effect as does a narrowed portal vein lumen. He found that after complete occlusion the spleen swells to three times its size, with resulting infar-

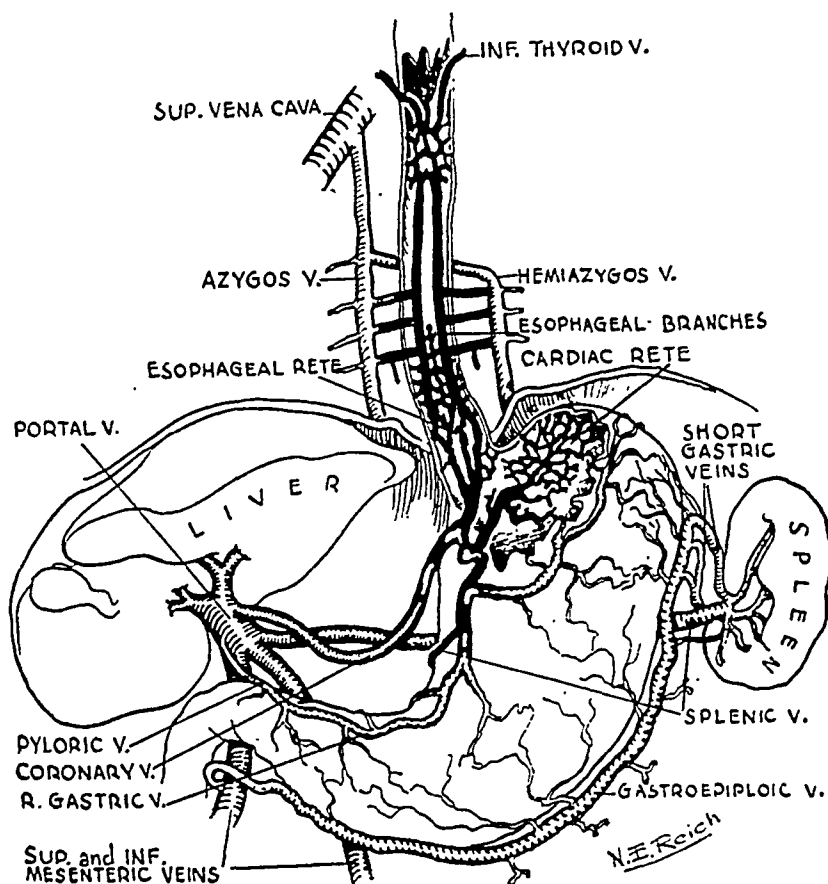


Fig. 4.—“Formation of varices in the esophagus and cardia. Note that the upper third of the stomach and esophagus has been exposed by removal of the anterior wall” (from Plotz and Reich<sup>10</sup>).

6. (a) Dock, G., and Warthin, A. S.: A Clinical and Pathological Study of Two Cases of Splenic Anemia, with Early and Late Stages of Cirrhosis, *Am. J. M. Sc.* **127**:24, 1904. (b) Klemperer, P.: Pathologic Anatomy of Splenomegaly, *Am. J. Clin. Path.* **6**:99, 1936. (c) Warthin, A. S.: The Relation of Thrombophlebitis of the Portal and Splenic Veins to Splenic Anemia and Banti's Disease, *Internat. Clin.* **6**:189, 1910. (d) Klemperer, P.: Cavernomatous Transformation of the Portal Vein: Its Relation to Banti's Disease, *Arch. Path.* **6**:353 (Sept.) 1928.

7. Menon, T. B.: Venous Splenomegaly: A Study in Experimental Portal Congestion, *J. Path. & Bact.* **46**:357 (March) 1938.

tion. After prolonged partial obstruction, little enlargement occurs. The spleen shows dilatation of the sinuses, distention of the pulp and trabecular veins and variable atrophy of the pulp, with slight fibrillary increase. Hyperplastic reactions are absent. His experiments tend to disprove, therefore, the long-held view that Banti's syndrome is due to a blockage of the portal vein. Some other factor is essential to induce proliferative changes in the spleen. An excellent description of the gross and microscopic pathology of the splenomegaly associated with sclerosis of the portal and splenic veins has been presented by Klemperer.<sup>9a</sup> Thompson<sup>8</sup> expressed the belief that the histopathologic changes in the spleen are the same in all cases of splenomegaly. They are similar in type to the changes described by Banti and others.

According to Adami,<sup>9</sup> the lesion of the vein is due to a strain fibrosis. The walls become thicker; the connective tissue is hypertrophied in all layers; the media presents tears and degeneration of the elastic tissue, and the intima contains connective tissue poor in nuclei. According to Simmonds<sup>10</sup> there is no inflammation and the process is analogous to that in atherosclerosis. In favor of this view is the resemblance of the portal vein to an artery by reason of its muscle fibers and the absence of valves. Benda<sup>11</sup> expressed disagreement with this view and suggested that a compensatory thickening develops on the basis of inflammatory as well as degenerative changes. In favor of this assumption may be cited the occurrence of mesenteric thrombosis with embolization of the portal vein in cases of postoperative abdominal infection, umbilical granuloma, infections and furunculosis during infancy, with resultant involvement of the portal system.

Gruber<sup>12</sup> showed the presence of congenital stenosis of the portal vein, which he attributed to the remains of some intra-abdominal pathologic condition acquired during intrauterine life. The mechanical effect of adhesions must not be overlooked. Wahlgren<sup>12</sup> presented 4 cases in which adhesions occurred between the spleen and the stomach and either narrowing of the vein from within or compression from without. He found the changes in the peripheral branches of the portal vein. The stenosis was followed by thrombosis and stasis.

8. Thompson, W. P.: Pathogenesis of Banti's Disease, *Ann. Int. Med.* **14**:255 (Aug.) 1940.

9. Adami, J. G., in Allbut, T. C., and Rolleston, H.: *System of Medicine*, New York, The Macmillan Company, 1910, vol. 1, p. 799.

10. Simmonds, cited by Benda, in Aschoff, L.: *Pathologische Anatomie*, Leipzig, Johann Ambrosius Barth, 1921, vol. 2, p. 91.

11. Benda, in Henke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1924, vol. 2, p. 829.

12. Wahlgren, A.: Contribution à l'étude des splénomégalias de l'enfance, *Acta pædiat.*, 1927, supp. 6.

Deposits of lipid are absent in the vein; hence, phlebosclerosis is probably produced by mechanical changes (portal hypertension), in contrast to the chemical causes which may operate in atherosclerosis. Wohlwill and Holm<sup>13</sup> proved the presence of a mechanical factor by inducing experimental portal hypertension in dogs. However, if cholesterol was then injected intravenously chemical changes were found to be superimposed.

According to the most recent investigation,<sup>14</sup> atheromatous change does not occur in veins and the adaptability of the portal vessels is not influenced by age, hypertrophy occurring in young subjects as frequently as in older ones.

According to Li,<sup>14</sup> two factors are concerned in the production of phlebosclerosis: (1) weakening of the venous wall by nutritional disturbance, degeneration of the media or inflammatory changes and (2) increase of venous pressure. Opinion is still divided as to which is more important and which occurs first<sup>15</sup> though in my estimation the organic changes precede the increased venous pressure. The phlebosclerotic changes of the portal system in portal hypertension are (1) muscular hypertrophy of the media, which occurs first, and (2) intimal thickening with development of longitudinal muscle beneath it.

#### CLINICAL DIAGNOSIS

The clinical course continues for a long time without hepatomegaly or ascites. Remissions occur and splenomegaly and anemia are present, while recurrent hemorrhages take place. Diagnosis may be suggested by the splenomegaly, which is decreased after a copious hemorrhage, establishment of collateral circulation (fig. 4)<sup>16</sup> and anemia. Hemorrhage occurred during the twelfth and twentieth years of disease in the patient whose case was reported by Hart,<sup>16</sup> and in the cases described by Gruber<sup>17</sup> death occurred thirteen and fourteen years after the first hemorrhage.

Bardach<sup>17</sup> reported a case in which examination revealed varicose veins in the lower portion of the esophagus and the fundus of the

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13. Wohlwill and Holm: Experimentelles zur Pfortadersklerose, Verhandl. d. deutsch. path. Gesellsch. **22**:235, 1927.

14. An excellent review and exacting study of the pathogenesis of portal system phlebosclerosis are to be found in an article by Li (Adaptation in Veins to Increased Intravenous Pressure, with Special Reference to the Portal System and Inferior Vena Cava, *J. Path. & Bact.* **50**:121 [Jan.] 1940).

15. Reich, N. E.: Portal System Thrombosis Occurring in Portal Hypertension, *Ann. Int. Med.*, to be published.

16. Plotz, M., and Reich, N. E.: Esophageal Varices in Portal Hypertension, Pathogenesis and Diagnosis by Roentgenography, *Am. J. Digest. Dis.* **5**:357 (Aug.) 1938.

17. Bardach, M.: Ein Fall von Pfortaderstenose und Myelothrombophlebitis im Kindesalter, *Arch. f. Kinderh.* **71**:270, 1922.

stomach. These may be recognized more frequently with a special roentgenographic technic.<sup>16</sup> Posthemorrhagic leukocytosis may obscure the picture. The thrombocytes may be decreased, and this change may in turn be accompanied by purpura.

#### DIFFERENTIAL DIAGNOSIS

Diseases which must be differentiated are: (1) Banti's syndrome, which offers the greatest difficulty in diagnosis but may be distinguished by the presence of a large liver, ascites, leukopenia, urobilinuria and progressive splenomegaly despite hemorrhages which occur much later in the disease; (2) peptic ulcer; (3) lymphoblastoma; (4) various types of purpura, and (5) disturbances of lipid metabolism (Gaucher and Niemann-Pick disease).

#### TREATMENT

Although a cure by recanalization is possible, the condition is progressive because of the increasing portal hypertension.

According to Freund and Schick,<sup>18</sup> the only rational treatment is the early removal of the spleen. This is said to reduce the volume of portal blood by 20 per cent.<sup>19</sup> However, the burden on the collateral circulation cannot be sufficiently removed by late splenectomy, since hematemesis and collateral circulation are found to persist. Hemorrhage from esophageal varicosities may be treated by surgical intervention, based on early diagnosis. At one time or another, McIndoe,<sup>20</sup> Kegaries,<sup>21</sup> Walters and associates,<sup>22</sup> Rousselot<sup>23</sup> and others<sup>24</sup> have recommended the following methods: (1) cauterization through an esophagoscope, (2) ligation of the coronary veins, (3) ligation of the vasa breva and (4) splenectomy, as previously suggested, to reduce the volume of portal blood.

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18. Freund, M., and Schick, B.: Typical Form of Splenomegaly in Childhood: Phlebrosclerosis of Portal Circulation, *J. Mt. Sinai Hosp.* **4**:221 (Nov.-Dec.) 1937.

19. Mayo, W. J.: Review of Five Hundred Splenectomies, *Ann. Surg.* **68**:409 (Sept.) 1928.

20. McIndoe, A. H.: Vascular Lesions of Portal Cirrhosis, *Arch. Path.* **5**:23 (Jan.) 1928.

21. Kegaries, D. L.: Venous Plexus of the Esophagus, *Surg., Gynec. & Obst.* **58**:46 (Jan.) 1934.

22. Walters, W.; Rowntree, L. G., and McIndoe, A. H.: Ligation of Coronary Veins for Bleeding Esophageal Varices, *Proc. Staff Meet., Mayo Clin.* **4**:146 (May 8) 1929.

23. Rousselot, L. M.: The Role of Congestion (Portal Hypertension) in So-called Banti's Syndrome, *J. A. M. A.* **167**:1788 (Nov. 28) 1936.

24. A fuller discussion of portal hypertension may be found in Greene, C. H.; Plotz, M., and Localio, S. A.: Liver and Biliary Tract, *Arch. Int. Med.* **61**:655 (April) 1939.

## COMMENT

In most cases primary portal phlebosclerosis occurs in young persons and is usually congenital. Sclerosis and narrowing of the portal system are present. Some investigators consider the sclerotic process of primary origin,<sup>8</sup> whereas others suggest primary stenosis with secondary sclerosis due to the portal hypertension. According to Li,<sup>14</sup> it is possible to have inflammatory change or sclerosis develop secondary to the increased venous pressure.

Portal hypertension is ordinarily seen in cases of atrophic cirrhosis, but it is recognized as a nonspecific syndrome and may develop in association with any condition in which there is obstruction to the portal flow.<sup>15</sup> This has led to a discussion of Banti's syndrome as a cause of congestive splenomegaly. The concept that Banti's disease, or splenic anemia, is the result of mechanical obstruction to the flow of blood within the portal system, which in turn is due to a variety of primary lesions, is gaining ground rapidly.<sup>25</sup> The interesting thing about phlebosclerosis is that it occurs early in life, before atrophic cirrhosis develops. One point in the clinical differentiation must be stressed. Although there are signs of portal hypertension (esophageal varices and splenomegaly), as in my case, there is no ascites. The absence of ascites is explained on the basis of normal serum protein, as it most frequently develops in patients with hepatic damage and hypoproteinemia. The early age also suggests that the stenosis is primary, with resultant hypertension and finally sclerosis, but this sequence is not proved. It is evident that splenomegaly may be explained on the basis of a congestive process secondary to portal hypertension.

## SUMMARY

A case of phlebosclerosis of the portal system is reported.

The use of the term primary portal phlebosclerosis is urged. The condition must be especially differentiated from Banti's syndrome, with which it has long been confused, although the pathologic changes in both may be undifferentiated. The onset at an early age; the absence of ascites and anemia; the presence of leukopenia, sclerosis and narrowing of the portal system, and the sequence of changes are in favor of the former.

It is my opinion that the changes of the venous wall resulting in stenosis of the portal system precede the portal hypertension.

75 Ocean Avenue.

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25. Rousselot, L. M.: Congestive Splenomegaly, *Bull. New York Acad. Med.* **15**:188 (March) 1939; footnote 23. Thompson.<sup>8</sup>

# Progress in Internal Medicine

## ALLERGY

A REVIEW OF THE LITERATURE OF 1941

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In arranging the many subheadings and topics which have developed in the study of allergy, one finds that some of these are concerned with the basic cause of trouble, others with the development of sensitiveness, others with the mechanisms by which symptoms result, others with the variety of symptoms, and, finally, still others with those changes which have nothing to do with the cause but represent the result or the effect of the primary disturbance.

Last winter I<sup>1</sup> prepared an informal talk along these lines, and the summary was published later in a small bulletin. The chart presented at that time has proved to be a useful arrangement of the various topics and so is presented again here, with some modification. First of all, this chart separates allergy as a study in immunology sharply from asthma, a study in physiology. It is true that often the two go together, so that the study of one involves the other, but, at the same time, it is worth repeating that asthma is not a disease entity, it is merely a symptom. The phrase "All is not allergy that wheezes" still holds. Furthermore, what applies to asthma applies also to hay fever, to eczema, to urticaria, to headache, indeed to all of the other symptoms which have become associated with the term "allergy." None of these symptoms depends always and inevitably on a state of hypersensitiveness.

Dragstedt<sup>2</sup> gives an outline for the study of allergic phenomena, discussing in order the allergen, the antibodies, the sensitized cells, the liberated products and the responsive tissues. Let us review the current literature in the light of my chart and with an eye on Dr. Dragstedt's outline.

## ALLERGY

### THE ALLERGIC STATE

The allergic state is real. That explains why it is that only a small proportion of those persons exposed to an occupational dust become sensitive to the new foreign substance; it explains why only a small

1. Rackemann, F. M.: Allergy: A Problem in Immunology; Asthma: A Problem in Physiology, *Bull. New England M. Center* 3:199, 1941.

2. Dragstedt, C. A.: Anaphylaxis and Allergy, *Ann. Int. Med.* 13:248, 1939.

proportion of the population has hay fever. Persons with an allergic constitution have the capacity for the development of sensitiveness. This is an old story illustrated by many experiences; another is the case reported by Way.<sup>3</sup> Dog asthma developed in a boy aged 15 and lasted until the dog died, four years later. For eleven years the young man was well, until, at the age of 30, he became interested in tropical fish. Asthma recurred in monthly attacks, which were found due to a newly acquired sensitiveness to the dust of dried water fleas (*Daphnia*) used as a fish food.

*The Problem \**

Allergy (Immunology)	Asthma (Physiology)
Nature of the allergic state	Spasm; edema
An "allergic person": one with a capacity for sensitiveness to develop, due to heredity (?), endocrine factors (?), vitamins (?)	Allergic reaction
Five criteria	"Intrinsic" asthma
Typical pathologic changes	Irritation from gas or cold air? (Reflex from nose?)
Multiple symptoms	Exudate
Family history of allergy	"Intrinsic" asthma
Eosinophilia	Bronchitis; tuberculosis; effect of gases
Positive cutaneous reactions	Obstruction
Development of sensitivity (Exposure; "low resistance")	Foreign body
Passive	Intrabronchial tumor
Placental transmission	Carcinoma
Transfusion	Gumma
Active	Extrabronchial tumor
Inhalation of dusts	Sarcoid
Ingestion of foods or drugs	Enlarged glands (Hodgkin's disease)
Injection of foreign substances (Chemistry of antigens)	Tuberculoma
Locus of symptoms	Emphysema
Mode of contact	"Pulmonary insufficiency"
Local injuries	Primary emphysema
Mechanism of symptoms	Secondary emphysema
Release of histamine by an antigen-antibody reaction (Acetylcholine?)	Chronic passive congestion
Factors changed as a result of symptoms	Cardiac: failure of the left side of the heart
Blood level of histamine	Cor pulmonale: failure of the right side of the heart
Eosinophil count	
Metabolism of salt and water	

\* Adapted from Rackemann.<sup>1</sup>

Heredity is dominant in this state, as emphasized again by Ratner and his associates.<sup>4</sup> Landsteiner and Chase<sup>5</sup> have been able to breed guinea pigs in such a way that one strain will be much more sensitive to poison ivy than another strain. In another experiment Chase<sup>6</sup> bred

3. Way, K. D.: Water Flea Sensitivity: Case Report, *J. Allergy* **12**:495, 1941.

4. Ratner, B.; Silberman, D. E., and Greenburgh, J. E.: Allergy in Childhood: IV. Does Heredity Determine the Age of Onset? *J. Allergy* **12**:272, 1941.

5. Landsteiner, K., and Chase, M. W.: Breeding Experiments in Reference to Drug Allergy in Animals, *Proc. Internat. Cong. Microbiol.*, 1940, p. 772.

6. Chase, M. W.: Inheritance in Guinea Pigs of the Susceptibility to Skin Sensitization with Simple Chemical Compounds, *J. Exper. Med.* **73**:711, 1941.



guinea pigs with a cutaneous sensitiveness to 2-4-dinitrochlorobenzene and then found that by careful breeding of his animals he could produce a strain of more sensitive and a strain of less sensitive guinea pigs. The last observation shows that heredity may be a factor in local cutaneous allergy as well as in the more general sensitiveness called "atopy."

What else is concerned? One thinks of internal secretions, but so far there is little evidence to suggest that one or the other of the endocrine glands is concerned with the allergic constitution. Barnes,<sup>7</sup> for example, studied the basal metabolism and the cholesterol content of the blood of 25 patients with allergy and 25 nonallergic control subjects, but the results were normal throughout both groups. The adrenal glands or variations in the output of epinephrine might be abnormal. Bloor and Bullen<sup>8</sup> have a new chemical method for determining the amount of epinephrine in the venous blood, and one can hope that later they will present data on the results of its use in a large series of cases.

The vitamins have been considered as a fundamental factor in the development of allergy and in the production of symptoms, and the problem is under investigation in the allergy laboratory of the Massachusetts General Hospital at this time. The literature on vitamin C in its relation to infectious disease as well as to anaphylactic shock and to allergy is voluminous and contains many papers dealing with experiments on animals but has relatively few observations on the concentration of ascorbic acid (vitamin C) in various clinical states. Recently, however, Goldsmith, Ogaard and Gowe<sup>9</sup> reported that for persons who had no condition known to be associated with subnormal vitamin C nutrition the ascorbic acid in the blood plasma varied from 0.07 to 2.40 mg. per hundred cubic centimeters, with a mean value of  $0.602 \pm 0.049$  mg. In 29 patients with asthma, however, this plasma ascorbic acid varied from 0.02 to 1.87 mg. per hundred cubic centimeters, with a mean value of  $0.410 \pm 0.051$  mg. The authors describe the good results which followed the administration of ascorbic acid in considerable amounts to their patients, the best method being to inject the material intravenously in doses as large as 1 Gm., a quantity which resulted in the raising of the blood level of ascorbic acid to 7.0 mg. per hundred cubic centimeters in about twenty minutes. After that it was comparatively easy to maintain a high level by the feeding of fairly large amounts

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7. Barnes, M. C.: The Thyroid in Allergy, *South. M. J.* **33**:1310, 1940.

8. Bloor, W. R., and Bullen, S. S.: The Determination of Adrenalin in Blood, *J. Biol. Chem.* **138**:727, 1941. Bullen, S. S., and Bloor, W. R.: Studies in Epinephrine: Recovery of Epinephrine Injected Intravenously and Subcutaneously, *J. Allergy* **12**:564, 1941.

9. Goldsmith, G. A.; Ogaard, A. T., and Gowe, D. F.: Vitamin C (Ascorbic Acid): Nutrition in Bronchial Asthma; An Estimation of the Daily Requirement of Ascorbic Acid, *Arch. Int. Med.* **67**:597 (March) 1941.

of the vitamin. It was interesting that patients with asthma could not maintain the level as well as could the nonasthmatic controls. As for the effect of treatment, one must recognize that when a large dose like this is injected intravenously in an asthmatic person, it is not impossible that the effect is more like that of a drug than like that of a food.

Cormia<sup>10</sup> reports that when massive doses of ascorbic acid were given first intravenously and then by mouth to patients in whom previously severe dermatitis had developed after the administration of arsphenamine an arsenical could be tolerated without difficulty. He could not show, however, that those patients whose blood level of vitamin C was low could be sensitized any easier than could those with a normal level of the vitamin in the blood. He reasoned that some factor in addition to the vitamin is involved. Bronfenbrenner and his associates<sup>11</sup> found that when guinea pigs are deficient in vitamin C sensitivity can be developed by feeding an antigen and that later shock will occur if the foreign protein is fed again. In the discussion of this paper Sulzberger called attention to his own previous observations that sensitiveness of the skin could be produced in certain lots of guinea pigs better than in others and that one of the differences was in the fodder on which the animals were fed. The interesting point, however, is that scurvy causes lesions in mucous membranes, which makes them more permeable and thus permits the passage of foreign protein into the blood. Meantime, however, Friedman<sup>12</sup> found that the muscles of scorbutic guinea pigs are much less sensitive to histamine than those of normal guinea pigs. Indeed, the minimal stimulating dose for scorbutic muscle in the Dale bath was of the order of a dilution of 1:10,000,000, whereas the normal muscle reacted to histamine in a dilution of 1:10,000,000,000. The latter was a thousand times more sensitive. Other papers deal with the use of vitamin C in clinical treatment, as a drug rather than as an essential food. One should note that ascorbic acid is a reducing agent.

#### DEVELOPMENT OF SENSITIVITY

Sensitization may be either active or passive.

*Passive Sensitization.*—The occurrence of this type of sensitization as a result of transfusion has been reported, but the cases are rare.

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10. Cormia, F. C.: Post Arsphenamine Dermatitis: The Relation of Vitamin C to the Production of Arsphenamine Sensitiveness and Its Use as an Adjunct to Further Arsphenamine Therapy in Patients with Cutaneous Hypersensitiveness to the Arsphenamines, *J. Invest. Dermat.* **41**:81, 1941.

11. Bronfenbrenner, J.; Hetter, D. M.; Love, F. M., and Burnett, J. M.: Experimental Alimentary Allergy and Its Prevention, *J. Allergy* **11**:466, 1940.

12. Friedman, H. J.: Effect of Vitamin C Deficiency upon Smooth Muscle Responsiveness to Non-Specific Stimulation, *J. Allergy* **12**:221, 1941.

Loveless<sup>13</sup> could collect only 6 reported cases, but to them she has added 3 cases in which experimental transfusions were made with blood from donors ill with ragweed hay fever. Within a few hours cutaneous tests, ophthalmic tests and nasal tests all gave positive reactions and skin-sensitizing antibodies were demonstrable in the blood serum of the recipients. The placental transmission of antibodies is much more likely to occur, and a new paper on the subject is one by Sherman, Hampton and Cooke,<sup>14</sup> The cord blood of newborn infants whose mothers were sensitive to pollen was tested for skin-sensitizing antibodies, but none was found. Extracts of the placenta in physiologic solution of sodium chloride failed to show antibodies. When, however, the cord serum was mixed with ragweed and then its effect compared with that of similar mixtures of control serum and ragweed, there was evidence of partial blocking. The retest of normal cutaneous sites passively sensitized with these mixtures gave less reaction with the cord serum than with the control blood, an indication of the presence of a mechanism by which the skin-sensitizing antibody was prevented (blocked) from combining with the admixed ragweed. Later on, however, when the infants were 3 to 6 months old, similar studies showed that the block has disappeared. The data in this experiment correspond with known facts concerned with the transmission of typhoid agglutinins and other immune principles and support the belief that the blocking effect depends on a true antibody.

*Active Sensitization.*—This type of sensitization is common enough. It may occur through the inhalation of dust or the ingestion of foods or drugs, or it may follow the injection of foreign substances. When exposure is slight, as in industry or in the household, it becomes evident that this exposure must continue over a definite interval before sensitiveness will develop. In my review of last year<sup>15</sup> two interesting papers were mentioned. Phillips<sup>16</sup> found that sensitiveness to the pollen of the sugar beet sufficient to cause hay fever did not occur in persons living near Phoenix, Ariz., until sugar beets had been cultivated in that part of the country for at least two years. Clarke and Leopold<sup>17</sup> reported that the

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13. Loveless, M. H.: Immunological Studies of Pollinosis: II. Passive Sensitization of Man Through Transfusion, *J. Immunol.* **41**:15, 1941.

14. Sherman, W. B.; Hampton, S. F., and Cooke, R. A.: The Placental Transmission of Antibodies in the Skin Sensitive Type of Human Allergy, *J. Exper. Med.* **72**:611, 1940.

15. Rackemann, F. M.: Allergy: Review of the Literature of 1940, *Arch. Int. Med.* **67**:207 (Jan.) 1941.

16. Phillips, E. W.: Time Required for the Production of Hay Fever by Spores of a Newly Encountered Fungus, Johnson Grass Smut, *J. Allergy* **12**:24, 1940.

17. Clarke, J. A., Jr., and Leopold, H. C.: Effect of Pollen Contact upon Age of Onset of Hay Fever, *J. Allergy* **11**:494, 1940.

interval for the development of hay fever was quite the same for immigrants arriving in this country as it was for native Americans. In the one case the interval began on landing; in the other it began at birth. Drug allergy as a whole will be discussed later, but many cases of this type are pertinent to the present topic, for they emphasize that exposure often continues for a time before symptoms appear.

**Sensitiveness Acquired by Inhalation:** This type of sensitivity was recognized by Bohner and associates<sup>18</sup> in a group of printers who used a spray of acacia as an "offset" in a printing process. Ten persons were observed, and it is interesting that they had been exposed for periods varying from two weeks to twelve months before asthma developed. King<sup>19</sup> has recognized another group of printers with precisely the same difficulties.

**Sensitiveness Acquired by Ingestion of Foods or Drugs:** This type is, of course, more common. Davidson and Bullowa<sup>20</sup> describe the case of a young Negro who was given 12 Gm. of sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) during an attack of pneumonia, with no particular reaction. Eleven days later, however, 5 Gm. of sulfamethylthiazole (2-[paraaminobenzenesulfonamido]-methylthiazole) was given, and within three hours generalized itching, with a scarlatiniform eruption, fever and chills, developed. Another case is reported by Kennedy and Finland,<sup>21</sup> but it is less typical. A woman aged 38 was treated with sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) for subacute bacterial endocarditis. Five days later a few petechiae appeared, and in two weeks the spleen became tender with a friction rub over it. In three weeks her leukocyte count was found to be only 1,200 per cubic millimeter, and she died of fatal granulocytopenia. In this case there was no history of her having taken any of the sulfanilamide drugs before. The attack was evidently a sort of serum disease.

**Sensitiveness Acquired by Injection of Foreign Substances:** This occurs more often than one would expect. The literature this year contains at least three references. Laws<sup>22</sup> reports the case of a woman aged 72 who was given thiamine hydrochloride daily for ten days and later every week. In about five months she noticed that each dose

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18. Bohner, C. B.; Sheldon, J. M., and Trenis, J. W.: Sensitivity to Gum Acacia, with a Report of Ten Cases of Asthma in Printers, *J. Allergy* **12**:290, 1941.

19. King, J. J.: Asthma and Allergic Rhinitis in Printers Due to Gum Arabic (Acacia) in Non-Offset Spray, *J. Med.* **22**:119, 1941.

20. Davidson, A., and Bullowa, J. G.: Acquired Hypersensitivity to Sulfapyridine and Sulfamethylthiazole, *New England J. Med.* **223**:811, 1940.

21. Kennedy, P. C., and Finland, M.: Fatal Agranulocytosis from Sulfathiazole, *J. A. M. A.* **116**:295 (Jan. 25) 1941.

22. Laws, C. L.: Sensitization to Thiamine Hydrochloride, *J. A. M. A.* **117**:176 (July 19) 1941.

produced a sneeze, and in seven months a dose was followed within thirty minutes by swelling of her eyes and lips, by generalized urticaria and, finally, by asthma. A cutaneous test with thiamine hydrochloride resulted in a large local reaction of the immediate urticarial type. Wiseman and Gillette<sup>23</sup> report the case of a patient with syphilitic meningitis who had received eighty doses of tryparsamide intravenously. After this treatment came an interval of two years without further attention, and then when the drug was resumed the second dose caused sudden amblyopia, without, however, other manifestations. Here was evidence of a specific sensitiveness localized to a particular tissue but artificially produced. Hansen<sup>24</sup> reports the case of a woman with asthma who was treated on five occasions by the injection of a 1 per cent solution of procaine hydrochloride into the stellate ganglion. The clinical results were excellent at first, but when the sixth dose was given respiratory paralysis and death occurred within ten minutes.

**Contact Dermatitis:** This must by its nature depend on local sensitiveness induced by previous local contacts. Zakon<sup>25</sup> had a patient who had worn an elastiglass wristband for eight weeks before a bullous dermatitis appeared, and there are many reports of similar cases except that in most of them the time interval is not stated. That local injury may determine the rate of development as well as the locus of sensitiveness is a point to be discussed later. In guinea pigs Landsteiner and Chase<sup>26</sup> were able to induce a sensitiveness to quinine by repeated applications of the drug in an oily vehicle. But it was induced more easily if a particular area had been inflamed by a local irritant. Finally, Bonnevie<sup>27</sup> calls attention to the danger of sensitization as a result of patch tests. This danger, however, is not great, for it was recognized in only 40 of 50,000 routine tests. Finally, one should note with Silverberg and Heimann<sup>28</sup> that cutaneous tests, whether made by the scratch or by the patch method, may give positive reactions, even though no clinical symptoms accompany them. A small series of fur workers

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23. Wiseman, J. R., and Gillette, D. F.: Drug Allergy with Special Reference to Tryparsamide, *New York State J. Med.* **41**:1, 1941.

24. Hansen, J. L.: Death from Procaine Hydrochloride in Connection with Infiltration of Procaine Hydrochloride into the Stellate Ganglion, *Ugesk. f. læger* **103**:159, 1941.

25. Zakon, S. J.: Bullous Dermatitis from Elastiglass, *Arch. Dermat. & Syph.* **43**:548 (March) 1941.

26. Landsteiner, K., and Chase, M. W.: Quinine Hypersensitivity in Guinea Pigs, *Proc. Soc. Exper. Biol. & Med.* **46**:223, 1941.

27. Bonnevie, P.: Etiologic-Pathogenetical Experience of Professional Skin Diseases and a View to Their Prophylaxis, *Acta dermat.-venereol.* **20**:632, 1939.

28. Silverberg, M. G., and Heimann, H.: Studies with Paraphenylenediamine in Fur Workers, *J. Invest. Dermat.* **4**:1931, 1941.

were given patch tests with paraphenylenediamine, and 4 of 10 gave positive reactions, even though they had never had any clinical signs of dermatitis.

The Chemistry of Hypersensitiveness: Several papers indicate that small differences in the chemical constitution of certain substances make a difference in the readiness with which sensitiveness to them is developed as well as in the production of symptoms. Arsenical dermatitis may result from the treatment with neoarsphenamine, but Schoch, Alexander and Long<sup>29</sup> found that if mapharsen was substituted no further trouble would follow. According to Franks and Fisher,<sup>30</sup> however, substitution of tryparsamide in the treatment of 2 patients produced recurrences of the dermatitis. The chemical relations are complex.

The sulfanilamide drugs are every day more important. Goodman and Arthur<sup>31</sup> observed a Negro in whom an eruption developed always in the same place after each dose of sulfanilamide. Sulfapyridine, however, was tolerated without ill effects. The other day I saw a patient of Dr. C. Lyons with an infection of the urinary tract whose symptoms were made worse by each and every one of the sulfanilamide drugs. In this case the sensitiveness was evidently due to a common basic factor and not to any particular or specific complex in the molecules. Cutaneous tests showed no reaction whatever to heavy suspensions of the various sulfanilamide drugs.

Direct chemical studies on different allergens reported during the year are few, and the results are still not entirely satisfactory. There has been much work done on the chemistry of ragweed, but so far no one has been able to isolate the active substance with any degree of assurance. In the allergy clinic of the Massachusetts General Hospital Dr. J. M. Newell<sup>32</sup> has studied the several fractions resulting from treatment of aqueous extracts of ragweed with various concentrations of ammonium sulfate or with various dilutions of alcohol. Each of these fractions was obtained in a relatively pure state by a technic which was as efficient as possible, the work being done in the Laboratory of Biological Chemistry at the Harvard Medical School through the courtesy of Prof. Edwin J. Cohn. In spite of the careful manipulation, the active

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29. Schoch, A. G.; Alexander, L. J., and Long, W. E.: Mapharsen in the Treatment of Forty Patients Following Arsphenamine Dermatitis, *Arch. Dermat. & Syph.* **42**:919 (Nov.) 1940.

30. Franks, A. G., and Fisher, S.: Sensitization to Arsenical Compounds, *Arch. Dermat. & Syph.* **42**:808 (Nov.) 1940.

31. Goodman, M. H., and Arthur, R. C.: Fixed Eruptions (Report of an Unusual Condition Due to Sulfanilamide), *Arch. Dermat. & Syph.* **43**:692 (April) 1941.

32. Newell, J. M.: Unpublished data.

principle demonstrable by cutaneous testing was present in most of the fractions, though varying somewhat in its quantity.

Stull, Sherman and Hampton<sup>33</sup> made an aqueous extract of ether-defatted ragweed and then precipitated it with a 50 per cent solution of ammonium sulfate. The precipitate was designated fraction 1 and was found to contain most of the nitrogen. When the material was fully saturated with ammonium sulfate a second precipitate was obtained, which was called fraction 2. This contained relatively little total nitrogen but still had a quantity which could be precipitated by phosphotungstic acid as protein nitrogen. Furthermore, this fraction gave a positive reaction to the Molisch test, which indicated the presence of carbohydrates. When these two fractions were tested on ragweed-sensitive patients the results were somewhat variable, although most patients reacted about equally to each of them. By crossed experiment, however, the authors found that each fraction had its own antigenic specificity, as well as some crossed relationship to the other fraction. Thus, when fraction 2 was mixed in a test tube with serum from a patient skin sensitive to both fractions, the mixture was still able to sensitize normal skin to fraction 1, an indication that neutralization was not complete. In a more recent paper Sherman and Hebal<sup>34</sup> report that when patients were more sensitive to fraction 2 than to fraction 1 general constitutional reactions were more likely to occur during treatment with the corresponding material.

Rockwell<sup>35</sup> digested ragweed extract with pepsin at a  $p_H$  of 7.5, but in spite of this treatment ragweed-sensitive persons still reacted well to the extract. This experiment shows, incidentally, that during oral treatment little if any of the pollen antigen can be destroyed by the enzymes of the stomach. Chemical studies on the cottonseed allergen gave results of a similar kind. Coulson, Spies and Stevens<sup>36</sup> separated three fractions by various methods, including treatment with trinitrophenol, and found that each of them elicited positive cutaneous reactions from cottonseed-sensitive patients. The allergic component seemed to be a heat-stable protein, which was evidently a preformed constituent of the cottonseed embryo.

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33. Stull, A.; Sherman, W. B., and Hampton, S. F.: Antigenic Fractions in Ragweed Pollen: I. Water-Soluble Fractions, *J. Allergy* **12**:117, 1941.

34. Sherman, W. B., and Hebal, S.: The Importance of Certain Antigenic Fractions of Ragweed Pollen in Relation to Constitutional Reactions During Treatment, *J. Allergy* **12**:605, 1941.

35. Rockwell, G. E.: The Effects of Enzymes on Ragweed Pollen and Studies on the Iso-Electric Point of Low-Ragweed Antigen, *J. Immunol.* **41**:225, 1941.

36. Coulson, E. J.; Spies, J. R., and Stevens, H.: The Immunochemistry of Allergens: I. Anaphylactogenic Properties of a Protein Component of Cottonseed, *J. Immunol.* **41**:375, 1941.

When Cooke and his colleagues<sup>37</sup> found that the reactions to tetanus toxoid were caused by the Witte peptone in the material, it occurred to them that possibly other primary and secondary proteoses might give rise to allergic reactions and so explain the presence of a clinical sensitiveness in the absence of a positive cutaneous reaction to the whole material. They therefore precipitated a variety of substances, first by half saturation and later by full saturation with ammonium sulfate. They used chicken meat, the whey and casein of milk, beef and beef fibrin, as well as egg albumin and wheat gliadin, and they found that many of these materials were quite capable of causing specific reactions when added to the isolated uteri of guinea pigs sensitized to them. In each case the reaction was specific for the particular proteose and quite different from the specificity of the original material. On the other hand, certain of the proteoses failed entirely to sensitize the animals. Further experiments along this line are awaited with interest, for they may help to explain the occurrence of clinical sensitiveness to a food in patients who do not give positive cutaneous reactions to the extract of that food. It may well be that the sensitiveness is to the split product and not to the whole food.

#### LOCUS OF SYMPTOMS

The locus of symptoms depends usually on the mode of contact. Chemicals of various sorts are used in industries and may cause trouble, usually in the form of a dermatitis, from direct contact. Pollens and dusts, like animal danders or the dust of kapok pillows, cause trouble through inhalation, and symptoms develop in the eyes, the nose and the chest (bronchi). But it is interesting to find that a substance like arsenic can produce symptoms of different sorts in different persons, even though they are all exposed in much the same way. Last winter I<sup>38</sup> reviewed the literature on drug allergy and found a tremendous variation in the manifestations of allergy to drugs of all sorts. Arsenic, for example, may produce a local contact dermatitis either from treatment of vaginitis with an arsenic compound or through contamination of the fingers with a solution of arsphenamine. The generalized dermatitis which occurs during antisyphilitic treatment is common enough. But then one finds that in other patients with similar treatment a reaction develops which is not a cutaneous disease at all but a blood dyscrasia,

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37. Cooke, R. A.; Hampton, S. F.; Sherman, W. B., and Stull, A.: Allergy Induced by Immunization with Tetanus Toxoid, *J. A. M. A.* **114**:1854 (May 11) 1940. Stull, A., and Hampton, S. F.: A Study of the Antigenicity of Proteoses, *J. Immunol.* **41**:143, 1941.

38. Rackemann, F. M.: Allergy, with Special Reference to Drug Allergy, *New England J. Med.* **224**:688, 1941.



like purpura or granulocytopenia. In some an attack of asthma appears. A condition of the same sort is being recognized already as caused by sensitiveness to sulfanilamide or to one of its relatives. Furthermore, why does one patient become sensitive to timothy and have hay fever in June, whereas the next one is sensitive to ragweed and has hay fever in August? One wonders about the possibility of local injury at the time of exposure; in the case of hay fever perhaps a bad cold or some other temporary disturbance lowers the resistance of the local mucous membrane in the nose. So far, the reason for all this is not at all clear, but the case reports in the field of drug allergy tend to broaden one's approach to the problem. The fact that certain tissues of the body can become more sensitive than others would seem to be established.

#### MECHANISM OF SYMPTOMS

Primarily, the symptoms of allergy depend on the reaction which takes place when the foreign substance reaches the specific antibodies in the sensitized cells. In the case of a local contact dermatitis, antibodies are not demonstrable in the blood and the hypersensitiveness is not transferable by means of the so-called reagin. In other, more typical conditions, such as hay fever and asthma, the fact that transfer is possible demonstrates a general sensitiveness of the whole body, with antibodies in the blood. So far it is thought that these antibodies are quite different from precipitins, but now comes evidence, presented by Cohen and Weller,<sup>39</sup> that the difference may be more apparent than real. Employing a colloidal suspension of collodion particles, they were able to treat aqueous extracts of pollen so that when serum from sensitive patients was added to the preparation a precipitate would result. In last year's review I<sup>15</sup> discussed the mechanism by which the good results of the treatment of hay fever might be explained. Sherman,<sup>40</sup> Loveless<sup>41</sup> and, more recently, Scully and Rackemann<sup>42</sup> have studied this question further, but, unfortunately, none of them has been able to demonstrate a relation between the degree of improvement and the concentration of the heat-stable blocking antibodies which appear to develop after treatment.

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39. Cohen, M. B., and Weller, R. R.: Precipitins in the Sera of Patients with Clinical Allergy, *J. Allergy* **12**:242, 1941.

40. Sherman, W. B.: Changes in Serological Reactions and Tissue Sensitivity in Hay Fever Patients During the Early Months of Treatment, *J. Immunol.* **40**: 289, 1941.

41. Loveless, M. H.: Immunological Studies of Pollinosis: I. The Presence of Two Antibodies Related to the Same Pollen Antigen in the Serum of Treated Hay Fever Patients, *J. Immunol.* **38**:25, 1940.

42. Scully, M. A., and Rackemann, F. M.: Studies on the Blocking Antibody of Cooke in the Treatment of Hay Fever, *J. Allergy* **12**:549, 1941.

How does the antigen-antibody reaction produce symptoms? Supposedly it does this by causing a liberation of histamine from the injured cells.

*Histamine.*—Last year the current literature on histamine and histaminase was reviewed <sup>43</sup> with some care, and the section ended with a quotation from Best and McHenry <sup>43</sup>: “There is no physiologic basis on which to rest the clinical use of histaminase.” Meantime, however, the work goes on, and a new series of papers has accumulated. A simple, well written and satisfactory summary of the relation of histamine to anaphylaxis and allergy is presented by Rose,<sup>44</sup> who touches on such topics as the distribution and state of histamine in the body, the effect of the administration of histamine, the comparison of histamine shock and anaphylactic shock, the evidence for the release of histamine in anaphylaxis and the possible relation of histamine to allergic phenomena. As for histaminase, the evidence for its effectiveness is conflicting. Some papers show that the enzyme histaminase is ineffective. Rose and Browne <sup>45</sup> have repeated their experiments on histamine shock in guinea pigs and now state that previous treatment with histaminase does not reduce the degree of histamine shock as previously reported. Alexander and Bottom <sup>46</sup> tried to protect guinea pigs against histamine shock and anaphylactic shock by treating them with histaminase, but with no success. On the other hand, Barlow and Hamburger <sup>47</sup> express the belief that a small percentage of their guinea pigs were protected against anaphylactic shock and against histamine shock by pretreatment with histaminase. Karady <sup>48</sup> also could prevent anaphylactic shock by pretreatment with histamine.

Knoll and Beinhauer <sup>49</sup> gave histaminase intravenously to sensitized guinea pigs just before a shocking dose of egg albumin, but the reaction occurred regardless of the preliminary treatment. The injection of histamine stimulates the secretion of acids in the stomach, and the action is easily studied. To dogs with a Heidenhain pouch Atkinson and

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43. Best, C. H., and McHenry, E. W.: Note on Histaminase, *Canad. M. A. J.* **43**:163, 1940.

44. Rose, B.: The Relation of Histamine to Anaphylaxis and Allergy, *McGill M. J.* **10**:2, 1940.

45. Rose, B., and Browne, J. S. L.: Effect of Histaminase Pretreatment on Histaminase Shock in Guinea Pigs, *J. Immunol.* **41**:409, 1941.

46. Alexander, H. L., and Bottom, D.: The Failure of Histaminase to Protect Guinea Pigs Against Histamine and Anaphylactic Shock, *J. Immunol.* **39**:457, 1940.

47. Barlow, O. W., and Hamburger, E.: The Influence of Histaminase on the Course of Anaphylaxis and Histamine Shock in Guinea Pigs, *J. Allergy* **12**:346, 1941.

48. Karady, E. S.: Histamine Tolerance and Anaphylactic Death in Sensitized Guinea Pigs, *J. Immunol.* **41**:1, 1941.

49. Knoll, A. F., and Beinhauer, L. G.: Experimental and Clinical Observations with Histaminase, *Arch. Dermat. & Syph.* **42**:896 (Nov.) 1940.

co-workers<sup>50</sup> gave histaminase, but they were unable to demonstrate any inhibition of the usual gastric response when histamine was given shortly afterward.

Clinical reports are a little more encouraging! With reference to cold allergy, Roth and Horton<sup>51</sup> repeat their assertion that treatment with histaminase can protect against the syndrome which follows the immersion of the hands in cold water. Cherry and Prickman<sup>52</sup> express the opinion that if histaminase is given within twenty-four hours after the onset of serum disease the severity of the symptoms is modified. Moreover, 9 patients were given the enzyme prophylactically at the time when the serum was administered: In 4 of them serum disease did not occur, and in the other 5 the reaction was mild. The difficulty is that "normal" serum disease is so irregular in its severity. Simon<sup>53</sup> had a more precise technic. Using the intradermal response to histamine as a test, he injected a solution of histaminase into the site sometimes before and sometimes after the injection of histamine, but in neither case could he show that histaminase was effective in modifying the response to histamine.

Studies on histamine itself are more interesting. First of all, it becomes clear that the effect of histamine is not related necessarily to the concentration in the blood. Rose<sup>54</sup> could not observe any regular increase in the histamine level of the blood during various allergic conditions. In certain acute states, such as an attack of angioneurotic edema, there was often a decrease in the value; in cases of asthma the values fluctuated to a considerable extent. Randolph and Rackemann<sup>55</sup> observed similar changes in a much smaller series of cases. Even when the symptoms, such as a rapid pulse, flushing, headache and low blood pressure, were produced directly by a dose of histamine administered subcutaneously, it was still impossible for Rose<sup>56</sup> to demonstrate any

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50. Atkinson, A. J.; Ivy, A. C., and Bass, V.: The Effect of Histaminase on the Gastric Secretory Response to Histamine, *Am. J. Physiol.* **132**:1, 1941.

51. Roth, G. M., and Horton, B. T.: Histaminase: Physiologic Effects on Man and Its Therapeutic Value in Medicine, *Bull. New York Acad. Med.* **16**:570, 1940.

52. Cherry, J. H., and Prickman, L. E.: The Treatment and Prevention of Serum Sickness by the Use of Histaminase, *Proc. Staff Meet., Mayo Clin.* **16**:38, 1941.

53. Simon, F. A.: Experiments with Histaminase, *J. Invest. Dermat.* **3**:299, 1940.

54. Rose, B.: Studies on Blood Histamine in Patients with Allergy: II. Alteration in the Blood Histamine in Patients with Allergic Disease, *J. Clin. Investigation* **20**:419, 1941.

55. Randolph, T. G., and Rackemann, F. M.: The Blood Histamine Level in Asthma and in Eosinophilia, *J. Allergy* **12**:450, 1941.

56. Rose, B.: Production of Symptoms by Subcutaneous Injection of Histamine Without Increase of the Blood Histamine, *Science* **92**:454, 1940.

increase of histamine in the peripheral blood. In a few cases of dermatographia, however, he<sup>57</sup> could show that after stroking the skin an immediate, though slight, rise in the histamine content of the blood occurred, but it was evanescent.

*Treatment with Histamine.*—Histamine may have a place as a therapeutic agent. Capps and Young<sup>58</sup> observed a patient who was extremely sensitive to light and exhibited urticaria and later circulatory collapse on exposure to a carbon arc light. Further exposure caused an increase of his gastric acids. Treatment with histamine produced a virtual cure. Farmer<sup>59</sup> had fair results in treating asthma and vasomotor rhinitis by increasing the tolerance to histamine. Alexander<sup>60</sup> makes an interesting observation: It is his experience that neither histamine nor histaminase has any value in the treatment of extrinsic allergy, in which the cause is a specific sensitiveness. But in other conditions, such as urticaria or, especially, intrinsic allergy, histamine may be helpful. The differences between the response of the two types of allergy raises the question whether the H substance (histamine-like substance) released in true allergy is qualitatively the same as that released in the other states.

*Ménière's Disease:* In cases of this disease histamine treatment may be of value. Horton,<sup>61</sup> of the Mayo Clinic, gave daily intravenous injections of 1.0 mg. of histamine base (2.75 mg. of histamine diphosphate or 1.88 mg. of histamine acid phosphate) diluted in 250 cc. of physiologic solution of sodium chloride, allowing it to run in slowly. In 49 patients the relief was prompt, and after a few days the intravenous method could be omitted and the gain maintained by subcutaneous injection of 0.1 to 0.2 mg. of histamine base two or three times a week. In 1939 Horton, MacLean and Craig<sup>62</sup> described a form of unilateral headache different from migraine. It is not inherited; it begins late, not early, in life, and it is not accompanied by nausea, by vomiting or by visual disturbances. The attacks begin and end suddenly and are of short, about an hour's, duration. It comes on usually at night, and the patient

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57. Rose, B.: Studies in Blood Histamine in Cases of Allergy: I. Blood Histamine During Wheal Formation, *J. Allergy* **12**:327, 1941.

58. Capps, R. B., and Young, R. H.: Hypersensitivity to Light: Studies on an Unusual Case Treated Successfully with Histamine, *J. Clin. Investigation* **19**:778, 1940.

59. Farmer, L.: Histamine Treatment of Allergic Diseases: I. Asthma and Vasomotor Rhinitis, *J. Lab. & Clin. Med.* **26**:802, 1941.

60. Alexander, H. L.: Treatment of Allergic Disorders with Histamine and Histaminase, *J. Lab. & Clin. Med.* **26**:110, 1940.

61. Horton, B. T.: The Use of Histamine in Ménière's Disease, *Surg., Gynec. & Obst.* **72**:417, 1941.

62. Horton, B. T.; MacLean, A. R., and Craig, W. McK.: A New Syndrome of Vascular Headache: Results of Treatment with Histamine; Preliminary Report, *Proc. Staff Meet., Mayo Clin.* **14**:257, 1939.

obtains relief by standing upright and by exercising. This type of headache is due to vasodilatation, not to constriction, of the cerebral vessels. It can be induced by histamine and relieved by the administration of epinephrine. It is relieved also by the application of cold water. This year Horton <sup>63</sup> reports on 72 patients suffering from what he now calls "histaminic cephalgia." Whereas histamine can induce the headache, small repeated doses given twice daily are an effective treatment. The doses should begin with 0.25 cc. from an ampule of histamine diphosphate, of which 0.275 mg. is equivalent to 0.10 mg. of histamine base, and the quantity should be reduced if flushing or headache occurs. After ten days (twenty doses), if all is well, the intervals can be lengthened so that maintenance doses are given twice, or maybe only once, a week. Of 51 patients with typical histamine cephalgia who were treated in this way, 48 had complete relief; the other 3 were not heard from. Baker <sup>64</sup> has recognized headache of this type in 15 patients and has given relief to 14 by treatment with histamine.

#### HAY FEVER

*New Pollen Surveys.*—Studies of this type are always welcome. Raddis <sup>65</sup> reports on pollens of Hawaii. The cycad tree gives off large quantities of pollen, but positive cutaneous reactions to it have not been observed. Grasses are present. The pollens of sugar cane, the mango and some of the palms cause some trouble in a few cases. Pollen counts are low. From Palestine Gutmann <sup>66</sup> writes that hay fever is only of the spring type, occurring from the end of February to the end of May, when the rain makes the grass grow. The island of Bermuda is relatively free of pollen. Gay, Curtis and Norris <sup>67</sup> state that the Bermuda cedar pollen is found on slides at all times of year except the fall months, September, October and November, but that the peak of the cedar pollination comes in March. In the summer, beginning in May, a few grasses are in flower, but not enough to cause trouble. There is no ragweed in Bermuda. Durham <sup>68</sup> has visited Alaska. In early July there is a little grass pollen in Juneau and Fairbanks, and in August

63. Horton, B. T.: The Use of Histamine in the Treatment of Specific Types of Headache, *J. A. M. A.* **116**:377 (Feb.) 1941.

64. Baker, B. M.: The Treatment of Periodic Headache by Injections of Histamine, *Tr. A. Am. Physicians* **55**:294, 1940.

65. Raddis, L. H.: Botanical Considerations of Some Pollens of Hawaii in Relation to Allergy, *Tr. Hawaii Territor. M. A.* **1**:75, 1939.

66. Gutmann, M. J.: The First Report on Hay Fever in Palestine, *J. Allergy* **12**:182, 1941.

67. Gay, L. N.; Curtis, H., and Norris, T.: A Pollen Survey of the Islands of Bermuda, *Bull. Johns Hopkins Hosp.* **68**:179, 1941.

68. Durham, O. C.: Atmospheric Allergens in Alaska, *J. Allergy* **12**:307, 1941.

the pine trees pollinate. A few fungi, mostly rusts, are to be found, but in Alaska there is no ragweed. From South America come two reports by Ruiz Moreno and his co-workers<sup>69</sup> and a paper by Walker and Carron.<sup>70</sup> The eucalyptus tree is important in Argentina, and further inland there is a bush, *Celtis tala*, which begins to pollinate in September and reaches a maximum in November and December. The weed *Parthenium* has a composite flower, with large amounts of pollen. Pratt and associates<sup>71</sup> have made a careful study of pollen in the Boston area, comparing the counts made at four different stations in the city. The resulting curves are similar, but they cannot be superimposed consistently, a fact which indicates that local vegetation and local wind currents around buildings and trees are important. Figures for pollen counts need not be taken always at their face value.

*Treatment of Hay Fever.*—There are new ideas on extracts for the treatment of hay fever. Naterman<sup>72</sup> precipitates his pollen extracts with tannic acid to make a "ragweed tannate," which he thinks gives better results. Spain and co-workers<sup>73</sup> add 4 parts of gelatin to 1 part of an aqueous extract of ragweed and report that the delayed absorption of the mixture results in a greater tolerance of large doses and so in better relief. It is of particular value for extremely sensitive patients. Meantime, Hansel<sup>74</sup> lays stress on the good results from coseasonal intracutaneous treatment of hay fever. He begins with tiny doses of dilute material and then for further injections increases the strength rather than the quantity. Seldom does he use material stronger than a dilution of 1:1,000.

Hay fever can occur in animals. At the 1940 meeting of the Association for the Study of Allergy, Wittich<sup>75</sup> exhibited moving pictures of a

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69. Castex, M. R.; Molfino, J. F., and Ruiz Moreno, G.: Primera contribución al estudio de la flora alergógena de la República Argentina; *Parthenium Hystero-phorus*, Bol. Acad. nac. de med. de Buenos Aires, 1940, p. 91. Castex, M. R.; Ruiz Moreno, G., and Solari, M. A.: Segunda contribución al estudio de la flora alergógena de la República Argentina; polen aéreo en la región de Bahía Blanca, Prensa méd. argent. **27**:2399, 1940.

70. Walker, H., and Carron, R. F.: Contribución al estudio de la polinosis en la República Argentina: nueva planta alergogena; el *Celtistala*, Día méd. (ed. espec. no. 6), 1940, p. 140.

71. Pratt, H. N.; Colmes, A.; Fromer, J.; Green, J. E.; Chafee, F. H., and Clapp, W. B.: Pollen and Mold Survey of Southeastern New England—1940, New England J. Med. **225**:533, 1941.

72. Naterman, H. L.: The Treatment of Hay Fever by Injections of Suspended Pollen Tannate, J. Allergy **12**:378, 1941.

73. Spain, W. C.; Fuchs, A. M., and Straum, M. B.: A Slowly Absorbed Gelatin-Pollen Extract for the Treatment of Hay Fever, J. Allergy **12**:365, 1941.

74. Hansel, F. K.: Coseasonal Intracutaneous Treatment of Hay Fever, J. Allergy **12**:457, 1941.

75. Wittich, F. W.: Spontaneous Allergy (Atopy) in the Lower Animal: Seasonal Hay Fever (Fall Type) in a Dog, J. Allergy **12**:247, 1941.

fox terrier which had all the symptoms of hay fever, as well as positive cutaneous reactions. Furthermore, excessive treatment resulted in a typical general reaction, which was relieved by epinephrine.

*Molds.*—These organisms need further study. Successful treatment of hay fever depends partly on the technic of dosage, but probably more on the specificity of the material used. In one group of ragweed-sensitive patients the results are satisfactory and easily obtained, but in another group treatment of the same sort, based on cutaneous reactions of much the same character, gives results which are not so good. It is the study of molds which suggests that these small organisms may complicate the picture and that, whereas late hay fever, for example, is due chiefly to ragweed, molds may play a part in its causation. Until recently the discrepancy between positive cutaneous reactions to molds and proof of clinical sensitiveness was rather striking, but now Pennington<sup>76</sup> describes a number of cases in which provocative tests made by applying the mold spores or their extracts directly to the nasal mucous membranes produced symptoms at once. She finds a considerable specificity: The provocative test may give a positive reaction for one mold but not for another. Meantime, Pennington<sup>77</sup> has made a mold survey for Nashville, Tenn., and found that *Alternaria* is most common. Pratt,<sup>78</sup> too, found that *Alternaria* causes the most reactions and that numerous crossed reactions occur among various species of the genus *Alternaria*. Specificity is not of a high degree. Chobot, Dundy and Schaffer<sup>79</sup> found that 27 per cent of 244 patients gave positive cutaneous reactions to *Alternaria* and that many of them reacted to other molds as well. Ophthalmic tests and nasal tests with the dry spores gave positive reactions in about one-half the cases, but in only a few instances was it possible to culture *Alternaria* from plates exposed in the patients' homes. Harris<sup>80</sup> subjected 22 patients skin sensitive to *Alternaria* to a "mold room" test, the air being sprayed with about 1 Gm. of *Alternaria* spores per 700 cubic feet (20 cubic meters), which were kept circulating by fans. Of 12 patients with typical histories of sensitivity to molds, asthma or rhinitis developed in 8 within ten to sixty minutes. Ten other patients with similar cutaneous reactions but without typical histories tolerated the mold room for an hour with no symptoms except

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76. Pennington, E. S.: A Study of Clinical Sensitivity to Air-Borne Molds. *J. Allergy* **20**:388, 1941.

77. Pennington, E. S.: A Study of the Incidence of Air-Borne Molds and of Skin Sensitivity to Molds, *South. M. J.* **33**:931, 1940.

78. Pratt, H. N.: Species Specificity of *Alternaria* in Asthma and Hay Fever, *J. Allergy* **12**:431, 1941.

79. Chobot, R.; Dundy, H., and Schaffer, N.: Relationship of Mold Reactions to Clinical Symptoms, *J. Allergy* **12**:46, 1940.

80. Harris, L. H.: Experimental Reproduction of Respiratory Mold Allergy, *J. Allergy* **12**:279, 1941.

in 1 case. When later the same patients were tested by asking them to inhale a small quantity of the mold powder from a flat toothpick held before the nostril, the results were quite the same as those obtained by the elaborate mold room method.

Waldbott and Ascher<sup>81</sup> describe rust and smut as major causes of allergic conditions of the respiratory tract. Schonwald<sup>82</sup> reports that the isolated spores of molds make a better antigen than does the extract of the whole felt from the surface of a broth culture. In the case of patients sensitive to flour mill dusts, Wittich<sup>83</sup> finds that the smuts which contaminate the grain are important factors in causing the symptoms. He, too, emphasizes the importance of careful study to find the precise cause of trouble, stating that if the dust and its extract are selected properly, hyposensitization is successful in 85 per cent of cases.

*Vasomotor Rhinitis.*—This term indicates a chronic form of hay fever-like symptom. Wittich<sup>84</sup> found 2 patients sensitive to the Mexican bean weevil, which caused trouble while they were working with peas and beans. A man employed in a spice factory had chronic vasomotor rhinitis because of paprika, according to Gelfand.<sup>85</sup> More important is the paper by Sternberg and Sorrell,<sup>86</sup> in which they present an outline list of some industries in which occupational asthma or vasomotor rhinitis is initiated. It is a useful compilation. Hansel<sup>87</sup> emphasizes once more the importance of staining specimens of the nasal and bronchial secretions to disclose eosinophile cells. On the other hand, Gillies<sup>88</sup> expresses surprise at the frequent presence of eosinophils in nasal polyps of patients who do not display evidence of allergy.

## ASTHMA

The theme in the first few paragraphs of this review was determined in part by the increasing number of papers dealing with asthma from causes other than allergy. Prickman and Moersch<sup>89</sup> describe the cases

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81. Waldbott, G. L., and Ascher, M. S.: Rust and Smut, Major Causes of Respiratory Allergy, *Ann. Int. Med.* **14**:215, 1940.

82. Schonwald, P.: Fungus Allergies, *Northwest Med.* **40**:17, 1941.

83. Wittich, F. W.: The Nature of Various Mill Dust Allergens, *Journal-Lancet* **60**:418, 1940.

84. Wittich, F. W.: Allergic Rhinitis and Asthma Due to Sensitization to the Mexican Bean Weevil (*Zabrotes Subfasciatus* Boh.), *J. Allergy* **12**:42, 1940.

85. Gelfand, H. H.: Vasomotor Rhinitis and Asthma Due to Paprika: Case Report, *J. Allergy* **12**:312, 1941.

86. Sternberg, L., and Sorrell, A. H.: Occupational Asthma and Vasomotor Rhinitis: An Outline of Some Common Industries Where These Symptoms Are Initiated, *New York State J. Med.* **41**:1649, 1941.

87. Hansel, F. K.: Allergy of the Upper and Lower Respiratory Tracts in Children, *Ann. Otol., Rhin. & Laryng.* **49**:579, 1940.

88. Gillies, A. D.: The Histology of Nasal Polypi, *M. J. Australia* **2**:149, 1940.

89. Prickman, L. E., and Moersch, H. J.: Bronchostenosis Complicating Allergic and Infectious Asthma, *Ann. Int. Med.* **14**:387, 1940.



of several patients who had asthma but who also had bronchostenosis, with local areas of collapse behind the obstruction. Bronchoscopy did much for them. A technic for studying the bronchi applied by Greenfield<sup>90</sup> is interesting. After the instillation of iodized poppyseed oil he measured the changes in caliber of certain bronchi during inspiration and expiration and found that in certain cases the changes in size were greater than normal whereas in other cases, of the "wet" type of bronchiectasis, the caliber remained the same in expiration as it was when the lung was fully distended. Chapman and Smith<sup>91</sup> made a similar study of iodized poppyseed oil shadows and present an interesting statistical analysis of observations on normal and on abnormal bronchi.

D'Abreu<sup>92</sup> observed through a bronchoscope the formation during an attack of asthma of the same fibrinous plugs which have been described before and which are so characteristic. Pratt<sup>93</sup> also reports finding them, at the autopsy of a child who died of asthma. Autopsies on patients who died of asthma are also described by Barla-Szabó<sup>94</sup> and by Cruciani and associates.<sup>95</sup> Craige<sup>96</sup> describes the pathologic observations on 7 women who died of asthma. Six of them exhibited bronchial plugs; all had many eosinophile cells in the bronchial wall, with thickening of the basement membrane and an increase in the number and size of the bronchial glands.

Loeffler's syndrome is a pneumonic infiltration, transitory in type and always associated with marked eosinophilia. It is not always accompanied by severe clinical illness. Cases are described by Santos<sup>97</sup> and by Freund and Samuelson.<sup>98</sup> Tuberculosis is usually the alternative diagnosis, but the differentiation is important. On the other hand, tuberculosis may in itself give rise to asthma, according to Urbach and

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90. Greenfield, J.: Bronchial Calibre Changes in Bronchiectasis, *J. Clin. Investigation* **19**:723, 1940.

91. Chapman, J., and Smith, H. D.: Diameters of Normal and Abnormal Bronchi: A Statistical Study, *Am. Rev. Tuberc.* **43**:504, 1941.

92. d'Abreu, A. L.: Asthmatic Attack Studied Through the Bronchoscope, *Lancet* **2**:421, 1940.

93. Pratt, H. N.: The Pathologic Physiology of Bronchial Asthma in Children, *New England J. Med.* **223**:626, 1940.

94. Barla-Szabó, L.: Pathologic Changes in Lungs of Persons Dying During Asthmatic Attack, *Orvosi hetil.* **84**:622, 1940.

95. Cruciani, A.; Etchemaite, P., and Gavlin, A.: Autopsia de una asmática muerta en crisis, *Prensa méd. argent.* **28**:247, 1941.

96. Craige, B., Jr.: Fatal Bronchial Asthma: Report of Seven Cases, *Arch. Int. Med.* **67**:399 (Feb.) 1941.

97. Santos, C.: Síndrome de Loeffler; pleuropneumopatía eosinofílica, *Rev. méd. latino-am.* **25**:508, 1940.

98. Freund, R., and Samuelson, S.: Transitory Infiltration of the Lung with Eosinophilia: Löffler's Syndrome, *Arch. Int. Med.* **66**:1215 (Dec.) 1940.

Loew,<sup>99</sup> who found 25 instances in a series of 452 asthmatic patients. Neumann<sup>100</sup> points out, however, that exogenic allergens may cause trouble even in the presence of tuberculosis and that the two diseases, pulmonary tuberculosis and asthma, do not by any means exclude each other.

Asthma resulting from the pressure of an extrabronchial tumor is listed in the table. A patient with sarcoidosis whose asthma was promptly relieved after treatment through the bronchoscope has been described by Benedict and Castleman.<sup>101</sup> Emphysema may in itself cause asthma. The literature is reviewed and 32 cases are described by Parker.<sup>102</sup> The difficulty here lies in the relation between the pathologic changes in the air spaces and those in the pulmonary vascular bed. Which of these comes first and leads to the other? Pulmonary arteriosclerosis, or Ayerza's disease, in the early stages is hard to recognize. In the advanced form cyanosis is typical. An interesting case is reported by Mason,<sup>103</sup> in which the patient died of rapid obstruction of the pulmonary arterioles, leading to failure of the right side of the heart. In this case the obstruction was due to emboli of small carcinoma cells arising from a primary tumor of the breast, for which radical mastectomy had been performed nineteen months previously. Similar is the case reported by Balboni,<sup>104</sup> in which multiple thromboses of the smaller pulmonary vessels were found. Incidentally, the author reviews the various pathologic conditions which can produce Ayerza's syndrome.

When emphysema is marked, blebs on the surface of the lung may rupture. This year, Caldwell<sup>105</sup> and Skinner<sup>106</sup> each add a case to the list of previous observations. Harkavy<sup>107</sup> describes a group of 8 patients with interstitial pulmonary infiltration, electrocardiographic changes and

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99. Urbach, E., and Loew, A.: Bronchial Asthma and Pulmonary Tuberculosis, *Am. Rev. Tuberc.* **62**:174, 1940.

100. Neumann, W.: Tuberkulose und Asthma, *Wien. klin. Wchnschr.* **53**:1021, 1940.

101. Benedict, E. B., and Castleman, B.: Sarcoidosis with Bronchial Involvement, *New England J. Med.* **224**:186, 1941.

102. Parker, R. L.: Pulmonary Emphysema: A Study of Its Relation to the Heart and Pulmonary Arterial System, *Ann. Int. Med.* **14**:5, 1940.

103. Mason, D. G.: Subacute Cor Pulmonale, *Arch. Int. Med.* **66**:1221 (Dec.) 1940.

104. Balboni, V. G.: Multiple Pulmonary Thrombi Associated with Cyanosis and Right-Sided Cardiac Hypertrophy, *New England J. Med.* **223**:22, 1940.

105. Caldwell, H. W.: Spontaneous Mediastinal Emphysema, *J.A.M.A.* **116**:301 (Jan. 25) 1941.

106. Skinner, H. J.: Asthma Complicated by Subcutaneous Emphysema in Children, *J. Pediat.* **18**:117, 1941.

107. Harkavy, J.: Vascular Allergy: Pathogenesis of Bronchial Asthma with Recurrent Pulmonary Infiltration and Eosinophilic Polyserositis, *Arch. Int. Med.* **67**:709 (April) 1941.

a high degree of eosinophilia. Six of them had a pleural effusion with eosinophils. Periarthritis nodosum was not proved in all the cases, but he considers the patients as having various degrees of a "hyperergic vascular reaction." Incidentally, Thompson and Paddock<sup>108</sup> found that if a drop of fresh blood is sealed under a cover glass with petrolatum and let stand for a week, Charcot-Leyden crystals will form, provided the blood contains many eosinophile cells. The crystals arise from the eosinophils.

*Treatment of Asthma.*—Unfortunately, there is little new in the treatment of asthma. Epinephrine and ephedrine are essential, and it is good to have a complete study of the nature, the origin and the physiology of epinephrine, as presented by Cori and Welch.<sup>109</sup> In their paper is an instructive table, which compares the chemical formulas of the members of this group of substances. Epinephrine, ephedrine and amphetamine benzedrine sulfate are closely related to each other, as well as to tyrosine and to phenylalanine. Epinephrine in oil is widely used, but not so widely as before. It is a suspension rather than a true solution, and so absorption of the drug is irregular, which leads to unexpected reactions in certain cases. Brown<sup>110</sup> has a good idea. He gives ephedrine by mouth in a special enteric-coated tablet which delays absorption for three or four hours—after bedtime. Amphetamine is more toxic than epinephrine. It has no bronchodilator effect and so is not useful in the treatment of asthma, according to Cameron and Kasanin,<sup>111</sup> who present a pharmacologic study of it. (The chemical formulas in this paper vary somewhat from those of Cori and Welch.)

*Theophylline and Its Relatives:* These compounds are often useful. Theophylline is a xanthine derivative related to caffeine and to theobromine. It is a diuretic and also a cardiac and cerebral stimulant, but its good effect in cases of status asthmaticus is not yet explained. Brown and Mark<sup>112</sup> review its action. Theophylline with ethylenediamine is being used widely in the treatment of asthma, not only in pills given by mouth in cases of simple asthma but, more important, as an effective emergency treatment for severe attacks in doses of  $3\frac{3}{4}$  grains (240 mg.) dissolved in 10 cc. of water and injected intravenously. Young and

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108. Thompson, J. H., and Paddock, F. K.: The Significance of Charcot-Leyden Crystals, *New England J. Med.* **223**:23, 1940.

109. Cori, C. F., and Welch, A. deM.: Glandular Physiology and Therapy: The Adrenal Medulla, *J.A.M.A.* **116**:2590 (June 7) 1941.

110. Brown, E. A.: A New Type of Medication to Be Used in Bronchial Asthma and Other Allergic Conditions, *New England J. Med.* **223**:843, 1940.

111. Cameron, W. M., and Kasanin, J.: A Pharmacologic and Clinical Reevaluation of Amphetamine (Benzedrine) Sulfate, *New England J. Med.* **224**:544, 1941.

112. Brown, C. L., and Mark, G. E., Jr.: The Therapeutics of Theophylline and Theophylline Derivatives, *Tr. Am. Therap. Soc.* **39**:68, 1941.

Gilbert<sup>113</sup> report that the drug can inhibit both histamine shock and anaphylactic shock in guinea pigs.

Theophylline monoethanolamine (theamin, Lilly) deserves more attention. In an excellent article Lamson and Bacon<sup>114</sup> describe its use in the treatment of asthma. There is evidence that caffeine can relax bronchial spasm as well as stimulate the respiratory center. "Not a few patients have discovered that a cup of hot black coffee may afford relief from asthma although sympathomimetic drugs may have failed." It was Prof. Paul Hanzlik who suggested that theophylline would be better than caffeine. It is effective when given by mouth. Lamson and Bacon lay great stress on dosage. In the case of ephedrine doses smaller than  $\frac{3}{8}$  grain (25 mg.) are often quite as good as doses twice as large. This is important, but in the case of theophylline monoethanolamine it is more important. More patients are relieved by doses of 1 or 2 grains (65 to 130 mg.) than by quantities as large as 5 or 6 grains (300 to 400 mg.), although sometimes these larger amounts are necessary. Untoward effects are not serious; most common are nausea and vomiting. What these authors emphasize is timely. All drugs should be used properly. In allergy, particularly, in which drugs are used for relief and not for treatment of the cause, results would be better if the drugs were used in quantities not larger than the smallest effective dose, regardless of the amount which the commercial pills contain. Half the pill may work as well.

**Intratracheal Injection of Iodized Oil:** This procedure was recommended a few years ago, but now the end result becomes apparent. Seibold<sup>115</sup> writes that in 641 cases the mortality rate increased 500 per cent in the first year of the use of iodized oil as a therapeutic measure. It may be justifiable to give oil once or twice for diagnostic purposes, but it should never be used for therapy.

**Expectorants:** These are discussed in an interesting paper by Holinger, Basch and Poncher.<sup>116</sup> They studied the  $p_H$  and the viscosity of sputum and found that these properties varied in different conditions. They were interested more in cases than in drugs. Oxygen is an anti-expectorant. It dries the secretions and increases their viscosity. Carbon

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113. Young, R. H., and Gilbert, R. P.: The Use of Theophylline with Ethylenediamine (Aminophyllin) for the Control of Bronchial Spasm, *J. Allergy* **12**:235, 1941.

114. Lamson, R. W., and Bacon, L. C.: Theophylline Mono-Ethanolamine: A Critical Study of Its Use in the Treatment of Asthma and Other Allergies, *J.A.M.A.* **116**:915 (March 8) 1941.

115. Seibold, G. J.: An Evaluation of Iodized Oil as a Therapeutic Agent in the Treatment of Bronchial Asthma, *Texas State J. Med.* **36**:386, 1940.

116. Holinger, P.; Basch, F. P., and Poncher, H. G.: The Influence of Expectorants and Gases on Sputum and the Mucous Membranes of the Tracheo-bronchial Tree, *J.A.M.A.* **117**:675 (Aug. 30) 1941.

dioxide, on the other hand, is an excellent expectorant, and the authors suggest that it be used more often. Whether the patient can tolerate concentrations of carbon dioxide up to the 5 or 10 per cent which the authors advise remains to be seen. The best effect apparently is obtained by combining oxygen with carbon dioxide and water (either as steam or as vapor from a mechanical humidifier). If cardiac function is good, carbon dioxide can be given even in the presence of cyanosis and severe dyspnea and may accomplish much.

### URTICARIA AND SERUM DISEASE

*Urticaria*.—There are two good papers this year which treat of urticaria in its broad aspects and in its relation to internal medicine. One is by Winkenwerder,<sup>117</sup> of Johns Hopkins University School of Medicine; the other by Baird,<sup>118</sup> of Boston. The literature on urticaria solaris is reviewed by Arnold.<sup>119</sup> The treatment of urticaria is always difficult, and histamine has been advised in the effort to increase the systemic tolerance to histamine. Alexander and Elliott<sup>120</sup> gave histamine in 49 cases, with satisfactory results in 19 cases. The method was to give a small intravenous dose of histamine, well diluted with saline solution and sufficient in quantity to produce slight flushing. When it works, the results are dramatic. Kahn and Grothaus<sup>121</sup> treated chronic urticaria on a basis of allergy, making cutaneous tests with strong extracts and then eliminating the corresponding foods. Cereals and fruits seemed to be the chief offenders, and the results were good in 17 of 18 cases. Stout and Kositchek<sup>122</sup> treated 58 patients by injecting a hypertonic solution of dextrose intravenously; 43 of them obtained satisfactory relief. Ten of these were patients with serum sickness, and one wonders whether the disease would not have terminated soon even without treatment. Angioneurotic edema of the hereditary type may be a separate disease entity, and I believe that the term Quincke's edema

117. Winkenwerder, W. L.: The Relationship of Urticaria and Angioneurotic Oedema to Internal Medicine, *Pennsylvania M. J.* **43**:1073, 1940.

118. Baird, P. C., Jr.: Medical Progress: Etiology and Treatment of Urticaria; Diagnosis; Prevention and Treatment of Poison-Ivy Dermatitis, *New England J. Med.* **224**:649, 1941.

119. Arnold, H. L., Jr.: Urticaria Solaris: Review of Literature and Report of a Case, *Arch. Dermat. & Syph.* **43**:607 (April) 1941.

120. Alexander, H. L., and Elliott, R. W.: Treatment of Chronic Urticaria with Intravenous Injections of Histamine, *J.A.M.A.* **114**:522 (Feb. 10) 1940.

121. Kahn, I. S., and Grothaus, E. M.: Treatment of Chronic Urticaria, Based on Successful Outcome of Seventeen out of Eighteen Cases, *South. M. J.* **33**:1086, 1940.

122. Stout, O. M., and Kositchek, R. J.: Parenteral Use of Hypertonic Dextrose for Relief of Pruritus and of Serum Sickness, *Arch. Dermat. & Syph.* **42**:802 (Nov.) 1940.

should be used to designate the condition, which occurs in families and which is not infrequently of serious prognostic import. Fineman<sup>123</sup> discusses the subject and describes 2 cases, in 1 of which the patient died of edema of the glottis.

*Serum Disease.*—This condition is closely related. Each year there are reports of serious, sometimes fatal, reactions after the injection of various therapeutic substances. For example, Ferguson<sup>124</sup> describes the case of a small boy who was given tetanus antitoxin because of deep abrasions received in an automobile accident. The antitoxin was given at 3:05 p. m., and in fifteen minutes severe dyspnea developed suddenly. The chest was in full inspiration. Artificial respiration was begun, and epinephrine was injected. In twenty-five minutes a large wheal developed at the site of the injection of the antitoxin, and the whole flexor surface of the forearm became red and edematous. More epinephrine was given, together with a diethylamine compound. His pulse improved for a few moments, but in fifteen minutes he was weaker again, and intravenous administration of a 5 per cent solution of dextrose was started. In forty-five minutes large quantities of frothy, blood-stained fluid began to pour from the lungs. The intravenous injection was stopped, and the patient's head was lowered to facilitate drainage. Oxygen was given, and the patient improved, but suddenly, at 5:30 p. m., two hours and a half after the antitoxin was given, he stopped breathing and could not be revived. The diagnosis at autopsy was "serum reaction, with pulmonary edema."

Newell and McVea<sup>125</sup> reviewed 500 cases in which tetanus antitoxin was given and found that in 11.8 per cent some type of reaction developed, usually a local reaction, which appeared within a few hours. Frank serum sickness occurred in only 4.4 per cent of cases. Wadsworth and Brown<sup>126</sup> observed a boy aged 11 who was given horse serum and in whom in twenty-four hours a high temperature developed, with rash, cyanosis and a rapid pulse—a severe reaction.

What is the real incidence of reactions like this? So far, there are no good figures, chiefly because the circumstances are so different in each case. When the dose is large, serum disease is more frequent. The condition is rarely fatal. When an acute, sometimes fatal, reaction occurs, it begins in a few minutes or, more rarely, in a few hours. Some-

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123. Fineman, A. H.: Hereditary Angioneurotic Edema, *Ann. Int. Med.* **14**:5, 1940.

124. Ferguson, R.: Fatal Serum Reaction, *Canad. M. A. J.* **43**:469, 1940.

125. Newell, C. E., and McVea, C.: The Prophylactic Use of Tetanus Antitoxin: The Analysis of Five Hundred Cases, *South. M. J.* **33**:962, 1940.

126. Wadsworth, G. H., and Brown, C. H.: Serum Reaction Complicated by Acute Carditis, *J. Pediat.* **17**:801, 1940.

times there is a history of previous treatment with the same material: The patient was actively sensitized. In most cases there is no such history and no particular reason to suspect trouble. Meantime, one reads that hundreds, perhaps thousands, of injections of serum have been given with no particular reaction. Perhaps, however, in these large series the physicians were aware of the danger and so were careful to ask a few crucial questions. Is there evidence of clinical allergy in the patient or in his family? Has he ever had reactions or peculiar episodes which were unexplained? As Rutstein, of the New York State Board of Health, and his associates <sup>127</sup> state: “. . . The incidence of immediate serum reactions in the patients with asthmatic histories was greater (45.5 per cent) than in those without such histories (29.6 per cent).” Reactions are always specific. Even if the patient does give a history of hay fever or of food allergy, it does not mean that serum is dangerous of necessity. The history is simply a warning of the danger and of the importance of taking all possible precautions—and a cutaneous test is easy to make.

*Tetanus Toxoid*.—This is being used on a large scale. The armies of France, Britain and Italy have used it routinely, and, according to Rouquies,<sup>128</sup> no case of tetanus among the immunized soldiers has been reported. Reactions, however, sometimes occur, particularly with the second dose. Cunningham,<sup>129</sup> Whittingham<sup>130</sup> and Parish and Oakley<sup>131</sup> report cases of anaphylactic shock following its use. The incidence seems to be about 1 per cent.

#### ALLERGY OF THE SKIN

“Eczema,” or “dermatitis” of the atopic type, with its characteristic distribution on the face, the neck and the cubital and popliteal spaces, with its cutaneous reactions of the immediate urticarial type and with a blood serum which can transfer the sensitiveness to a normal person, is quite comparable to hay fever and asthma. Little new is said about it this year, though Hill<sup>132</sup> discusses the problem well.

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127. Rutstein, D. D.; Rogers, E. S., and McCaffrey, I.: The Significance of a History of Asthma with Reference to Serotherapy, *New England J. Med.* **225**: 368, 1941.

128. Rouquies, L.: Le tétanos la vaccination et la séro-vaccination, *Presse méd.* **48**:497, 1940.

129. Cunningham, A. A.: Anaphylaxis After Injection of Tetanus Toxoid, *Brit. M. J.* **1**:522, 1940.

130. Whittingham, H. E.: Anaphylaxis Following the Administration of Tetanus Toxoid, *Brit. M. J.* **1**:292, 1940.

131. Parish, H. G., and Oakley, C. L.: Anaphylaxis After Injection of Tetanus Toxoid, *Brit. M. J.* **1**:294, 1940.

132. Hill, L. W.: Eczema in Infants and Young Children, *New England J. Med.* **223**:624, 1940.

Contact dermatitis, in which the sensitiveness is localized to certain portions of the skin and in which trouble comes not through the blood stream underneath but through direct contact on the surface, is more dramatic, since discovery of the cause of trouble leads usually to a perfect cure. There are numerous reports. Bauer<sup>133</sup> describes the case of a physician with localized dermatitis caused by his elastiglass wrist watch strap. Hollander<sup>134</sup> observed 3 patients with dermatitis of the face due to contact with nail lacquer. In two other papers, he<sup>135</sup> reports, first, on a dermatitis due to the rubber sponge which a woman used as a powder puff—patch tests with the face powder itself were quite negative—and, second, on a dermatitis due to the stain on the handle of a kitchen knife. Brown and Brown<sup>136</sup> had a patient who was sensitive to mangos, and Schwartz and Warren<sup>137</sup> had one who was sensitive to copperweed. Walters and Stern<sup>138</sup> incriminate the dextrin used in a cigaret factory as an adhesive for tax stamps. Guy and Jacob<sup>139</sup> found that girls employed in capping whisky bottles had a dermatitis from parachlorometacresol, the shipping fluid in which the caps were preserved. After the caps were washed no new cases of the dermatitis appeared. In a canning factory, Vickers<sup>140</sup> found that 32 of 205 workers showed positive reactions in patch tests to the carrot extract which caused their dermatitis. Another occupational disease was arsenic dermatitis, found in tobacco workers. Barksdale<sup>141</sup> was able to trace the trouble to the insecticide used in destroying plant parasites. Stewart's<sup>142</sup> patient had

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133. Bauer, W. W.: Delayed Appearance of Reaction to Elastiglass Wrist Watch Strap, *J. A. M. A.* **116**:404 (Feb. 1) 1941.

134. Hollander, L.: Nail Lacquer Dermatitis, *J. A. M. A.* **115**:1714 (Nov. 16) 1940.

135. Hollander, L.: Dermatitis Due to a Face Powder Conveyor, *J. A. M. A.* **115**:2271 (Dec. 28) 1940; Dermatitis Due to a Stain on the Wooden Handle of a Kitchen Knife, *Arch. Dermat. & Syph.* **43**:381 (Feb.) 1941.

136. Brown, A., and Brown, F. R.: Mango Dermatitis, *J. Allergy* **12**:310, 1941.

137. Schwartz, L., and Warren, L. H.: Dermatitis Caused by Contact with Copperweed (*Oxytenia Acerosa*), *J. Allergy* **12**:63, 1940.

138. Walters, J. D., and Stern, E. C.: Dermatitis Due to Dextrins Used as an Adhesive on Tax Stamps, *J. A. M. A.* **116**:1518 (April 5) 1941.

139. Guy, W. H., and Jacob, F. M.: Dermatitis Due to Parachlorometacresol, *J. A. M. A.* **116**:2258 (May 17) 1941.

140. Vickers, H. R.: The Carrot as a Cause of Dermatitis, *Brit. J. Dermat.* **53**:52, 1941.

141. Barksdale, E. E.: Cutaneous Manifestation from Tobacco, *J. A. M. A.* **115**:672 (Aug. 31) 1940.

142. Stewart, C. D.: Dermatitis Due to Mesquite Wood, *Arch. Dermat. & Syph.* **42**:937 (Nov.) 1940.



trouble from mesquite sawdust. Jordon, Dolce and Osborne<sup>143</sup> emphasize the role of soaps in causing dermatitis on the hands of housewives.

Poison ivy sensitivity is of greater practical importance and has now been studied more extensively. Shelmire<sup>144</sup> reviews the botanic classification. The small climbing vines are called *Toxicodendron radicans*, and the same plants may also grow into small shrubs. A variety, however, has large oaklike leaves and is called *Toxicodendron quercifolium*. In California a third variety is called *Toxicodendron diversilobum*. Poison sumac, *Toxicodendron vernix*, is obviously different from the other plants. In each case, the milky sap, when applied in crude form to the skin of a normal person, is irritating enough to cause necrosis and eschars. Shelmire finds that patients sensitive to any one of these plants are sensitive also to the others. He made experiments in destroying the poison and found that neither by drying in air, nor by soaking in water nor by boiling could he remove the active principle. Clothing once contaminated remains poisonous. In discussion of this paper, Sulzberger makes a pertinent remark, "If this is so, why doesn't every one have poison ivy dermatitis all the time?" It is a good question, to be answered presumably by the fact that not all people are as exquisitely sensitive as the subjects which Shelmire used to test the activity of his preparations. In another paper, Shelmire<sup>145</sup> gives a useful technic for extracting the resins of various plants. Mature plants are gathered, dried on paper in a darkened room, broken or ground and packed in a jar. Ether is added and allowed to stand for twenty-four hours, after which the ether extract is allowed to evaporate and the residue is taken up in various volumes of acetone. This residue is then preserved in small cork-stoppered bottles. The extract is applied by touching the moistened end of the cork to the unbroken skin of the patient, and the acetone is allowed to evaporate. The sites mark themselves by their green color, and no dressing or cover is necessary. Sixty tests can be made in five minutes. If the patient is sensitive, a localized area of dermatitis will appear at the test site in two or three days. Patch tests with poison ivy give positive results in many patients. Greenberg and Mallozzi<sup>146</sup> observed 119 positive reactions in a group of 278 men. Of those who reacted posi-

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143. Jordon, J. W.; Dolce, F. A., and Osborne, E. D.: *Dermatitis of Hands in Housewives: Role of Soaps in Its Etiology and Methods for Its Prevention (Especially by Use of Soap Substitutes)*, J. A. M. A. **115**:1001 (Sept. 21) 1940.

144. Shelmire, B.: *The Poison Ivy Plant and Its Oleoresin*, J. Invest. Dermat. **4**:337, 1941.

145. Shelmire, B.: *Contact Dermatitis from Vegetation*, South M. J. **33**:337, 1940.

146. Greenberg, S., and Mallozzi, E.: *Experiments in Poison Ivy Sensitivity: Effects of Specific Injections on the Level of Sensitivity to Quantitative Patch Tests and on Clinical Susceptibility*, Arch. Dermat. & Syph. **42**:290 (Aug.) 1940.

tively, clinical dermatitis developed in 39 per cent on exposure, but of those whose reactions to patch tests were negative, only 9 per cent had trouble. Reuter and White<sup>147</sup> have studied the interval between exposure and the onset of symptoms. A small patch about 2 cm. square was cut from a fresh poison ivy leaf and rubbed on the skin, and then a dry dressing was applied. Among the 23 subjects studied the incubation period varied from one to eighteen days. The duration of the lesion varied from two to twenty-one days.

Specific treatment of poison ivy sensitiveness remains unsatisfactory. At the meeting of the Association for the Study of Allergy in June 1940 Shelmire<sup>148</sup> gave a fascinating account of a nurse who was exquisitely sensitive to poison ivy. Treatment by mouth was begun with 1 drop of ivy oleoresin in corn oil in a dilution of 1:200. In three months the nurse could take 15 drops of the oleoresin in a dilution of 1:50. Patch tests were positive, though the reactions were less intense than those which preceded the therapy. When they had healed, the dose was increased rapidly to 60 drops of oleoresin in a dilution of 1:25. Four days later rather severe pruritus and developed, the healed patch test sites flared and a red, blotchy, generalized rash appeared. (Silvers<sup>149</sup> reports the case of a woman who chewed poison ivy leaves. A severe eruption developed in her mouth and about the anus, but there were no gastrointestinal symptoms.) More treatment made the rash worse but did not cause any changes in blood pressure, in the results of urinalysis or in blood counts. When in two weeks the rash had faded a further patch test with the oleoresin in a dilution of 1:100 resulted in erythema, with slight swelling: the nurse could actually pick poison ivy and crush the leaves without trouble. Later the oral administration was resumed and continued until she was taking each day more than 25 cc. of the oleoresin in corn oil in a dilution of 1:25 (55 capsules containing 15 drops each). Patch tests produced a slight erythema, as before, but actual exposure to poison ivy remained harmless.

#### OTHER MANIFESTATIONS OF ALLERGY

The wide variety of other allergic reactions was mentioned earlier in this review. They provide evidence that one kind of tissue may be more sensitive than another. Here are some further examples.

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147. Reuter, R. J., and White, S. F.: Susceptibility to and Latency of Poison-Ivy Dermatitis, *New England J. Med.* **224**:460, 1941.

148. Shelmire, B.: Cutaneous and Systemic Reaction Observed During Oral Poison Ivy Therapy, *J. Allergy* **12**:252, 1941.

149. Silvers, S. H.: Stomatitis Venenata and Dermatitis of the Anal Orifice from Chewing Poison Ivy Leaves, *J. A. M. A.* **116**:2257 (May 17) 1941.

Perera<sup>150</sup> observed a patient who had sensitiveness of the conjunctivas to nupercaine. Miller<sup>151</sup> recognized that the lesions of the lips (cheilitis) of a young woman were due to the vapors of the oil of cinnamon in bubble gum. A patch test and, later, a fume test were both positive. Cohen and Brodsky<sup>152</sup> gave 0.50 cc. of tincture of digitalis to a young woman, and within one-half hour generalized erythema, with urticaria, developed. The second and third doses, given some days later, resulted in a similar violent general reaction.

Dermatitis medicamentosa is always interesting, and the subject is reviewed by Brunsting<sup>153</sup> and also by Burckhardt.<sup>154</sup>

Blood dyscrasias caused by allergy should be recognized, for their proper diagnosis may be of crucial importance. Thomas and Forsythe,<sup>155</sup> at the Cleveland Clinic, found that in 10 of 64 patients purpura haemorrhagica depended on allergy. In each case one or more allergic manifestations were present. On the other hand, treatment on the basis of allergy did not bring relief in all cases. Loveman and Simon<sup>156</sup> report the case of a patient in whom erythema nodosum was clinically dependent on her sensitiveness to sulfanilamide. However, all methods of testing her with the drug gave negative results. Patch tests and intradermal tests with tissue extract from a nodule and with blood serum were all negative both on normal and on previously sensitized areas.

Allergic reactions to insulin, to extracts of liver, pituitary gland and pancreas or to estrogens and other endocrine substances are not uncommon, and a large literature has developed concerning this. It is reviewed in an excellent study by Harten and Walzer.<sup>157</sup> Their paper contains 169 references. To their list of cases a few more recently reported ones can be added. Crip<sup>158</sup> observed 2 patients sensitive to pancreatic tissue

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150. Perera, C. A.: Ocular Sensitivity to Nupercaine, *Arch. Ophth.* **24**:344 (Aug.) 1940.

151. Miller, J.: Cheilitis from Sensitivity to Oil of Cinnamon Present in Bubble Gum, *J. A. M. A.* **116**:131 (Jan. 11) 1941.

152. Cohen, R. V., and Brodsky, M. L.: Allergy to Digitalis, *J. Allergy* **12**:69, 1940.

153. Brunsting, L. A.: Dermatitis Medicamentosa, *Minnesota Med.* **24**:169, 1941.

154. Burckhardt, W.: Allergic Toxicodermatoses: I. Eczema; II. Drug Exanthemata; III. Urticaria; IV. Purpura; V. Erythemas, *Dermatologica* **79**:175, 1939.

155. Thomas, J. W., and Forsythe, J. R.: Allergy in Relation to Purpura, *J. Lab. & Clin. Med.* **26**:1105, 1941.

156. Loveman, A. B., and Simon, F.: Erythema Nodosum from Sulfanilamide, *J. Allergy* **12**:28, 1940.

157. Harten, M., and Walzer, M.: Annual Review: Allergy to Insulin, Liver, Pituitary, Pancreas, Estrogens, Enzymes, and Similar Substances, *J. Allergy* **12**:72, 1940.

158. Crip, L. H.: Allergy to Pancreatic Tissue Extract, with Report of Two Cases, *J. Allergy* **12**:154, 1941.

extract. They gave positive cutaneous reactions to the material, and it was possible to detect antibodies in their serum, since passive transfer to a normal person was successful. Andrews<sup>159</sup> reports the case of a patient who was sensitive to liver extract and then was desensitized by daily injections of increasing size. Wechsler, Farmer and Urban<sup>160</sup> report the case in which a patient's reaction to insulin simulated an attack of coronary occlusion but when positive cutaneous reactions were given to many brands of insulin, including crystalline insulin, the diagnosis became clearer and the prognosis better. Reactions to insulin in patients with diabetes are not common. Yasuna<sup>161</sup> reviewed the case records of 3,323 diabetic patients admitted to the Boston City Hospital since 1929 but did not find any cases of generalized insulin sensitiveness. Also he studied the literature but could find a total of only 12 cases, and it is interesting that in 8 of these there was evidence of allergy other than the sensitivity to insulin.

Allergic gastritis is mentioned by Hansen,<sup>162</sup> with proper comment on the importance of a family history and of other evidences of allergy in the same patient. Recurrent vomiting in children may be of allergic origin, according to Fries and Jennings.<sup>163</sup> Ménière's disease has been mentioned earlier in connection with the experience of Horton<sup>61</sup> that histamine given intravenously may be a successful method of treatment. Bowen<sup>164</sup> observed 14 patients who suffered from allergic conjunctivitis. The family history was positive; about one half of them had hay fever, the others being sensitive to cosmetics, drugs or foods. He points out wisely that vernal catarrh is a form of contact dermatitis, a local sensitiveness of the conjunctivas, and is so not likely to give positive cutaneous reactions comparable to those obtained in cases of atopic allergy. Cormia<sup>165</sup> expresses the belief that food sensitivity can aggravate acne vulgaris and states that he helped 70 per cent of his patients to obtain relief by changing their diets.

The list of papers mentioned here is long, but it is in no way complete. As in previous reviews, much selection has been necessary. Many important articles, as well as several whole topics, have been omitted. To include them all takes space and is not essential. The object has

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159. Andrews, C. T.: Allergic Reaction to Liver Extract, *Lancet* **1**:664, 1941.

160. Wechsler, H. F.; Farmer, L., and Urban, J. A.: A Case of Insulin Allergy Simulating Coronary Occlusion, *J. Lab. & Clin. Med.* **26**:1090, 1941.

161. Yasuna, E.: Generalized Allergic Reactions to Insulin: Review of the Literature, with Report of a Case, *J. Allergy* **12**:295, 1941.

162. Hansen, K.: Gastritis allergica, *Deutsche med. Wchnschr.* **67**:197, 1941.

163. Fries, J. H., and Jennings, K. G.: Recurrent Vomiting in Children, *J. Pediat.* **17**:458, 1940.

164. Bowen, R.: Allergic Conjunctivitis, *South. M. J.* **34**:184, 1941.

165. Cormia, F. E.: Food Sensitivity as a Factor in the Etiology of Acne Vulgaris, *J. Allergy* **12**:34, 1940.

been to call attention to those papers which seemed to throw light on fundamental principles and not to present long lists of isolated observations. The review may be of some value to those whose primary interest is allergy, but I hope that it will draw the attention of physicians who work chiefly in other fields. I hope that they will at least turn the pages to see the number of topics which apply to their own practice.

Allergy is a practical problem, and its manifestations are encountered in any and all fields of medicine. The ophthalmologist sees vernal catarrh; nasal polyps worry the rhinologist; nerve lesions complicate serum reactions, and intestinal urticaria is confused with appendicitis. Bladder allergy is described. The practicing physician sees allergic reactions in one form or another almost every day. Antitetanus serum is given to large numbers of persons on slight provocation. Then all physicians give drugs. Each year come new drugs, with complicated formulas and with actions which are known and good, but with side effects which are less known and which are not so good. If the physician will only think of allergy, he will have made a gain in his understanding of the case at hand. If, then, he knows something of the principles of allergy, he will appreciate its limitations and will distinguish what allergy can do from what it cannot do. He will know that to be really valid a diagnosis based on allergy must also be based on common sense.

263 Beacon Street.

## News and Comment

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**Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation.**—Thirty-five grants were made by the trustees of the Ella Sachs Plotz Foundation for the Advancement of Scientific Investigation during 1941, one being a continued annual grant.

In the eighteen years of its existence the foundation has made four hundred and twenty-nine grants, which have been distributed to investigators in Arabia, Argentina, Austria, Belgium, Brazil, Canada, Chile, China, Czechoslovakia, Denmark, Egypt, Estonia, Finland, France, Germany, Great Britain, Greece, Hungary, India, Iraq, Italy, Latvia, Lebanon, Netherlands, North Africa, Norway, Palestine, Peru, Poland, Portugal, Rumania, South Africa, Sweden, Switzerland, Syria, Venezuela, Yugoslavia and the United States.

In their first statement regarding the purposes for which the fund would be used, the trustees expressed themselves as follows:

"1. For the present, researches will be favored that are directed towards the solution of problems in medicine and surgery or in branches of science bearing on medicine and surgery.

"2. As a rule, preference will be given to researches on a single problem or on closely allied problems; it is hoped that investigators in this and in other countries may be found, whose work on similar or related problems may be assisted so that more rapid progress may be made possible.

"3. Grants may be used for the purchase of apparatus and supplies that are needed for special investigations, and for the payment of unusual expenses incident to such investigations, including technical assistance, but not for providing apparatus or materials which are ordinarily a part of laboratory equipment. Stipends for the support of investigators will be granted only under exceptional circumstances."

In the past few years the policy outlined in paragraph 2 has been neglected. During the present great need for funds, grants will be given in the sciences closely related to medicine without reference to special fields. The maximum size of grants will usually be less than \$500.

Requests for grants to be held during the year 1942-1943 must be in the hands of the executive committee before April 1942. Letters asking for aid must state definitely the qualifications of the investigator, give an accurate description of the research, the size of the grant requested and the specific use of the money to be expended. In their requests for aid, applicants should state whether or not they have approached other foundations for financial assistance. It is highly desirable to include letters of recommendation from the directors of the departments in which the work is to be done. Only requests complying with the conditions cited will be considered.

Requests should be sent to Dr. Joseph C. Aub, Collis P. Huntington Memorial Hospital, 695 Huntington Avenue, Boston, Mass., U. S. A.

**Mississippi Valley Medical Society 1942 Essay Contest.**—Each year the Mississippi Valley Medical Society offers a cash prize of \$100, a gold medal and a certificate of award for the best unpublished essay on any subject of general

medical interest (including medical economics) and practical value to the general practitioner of medicine. Certificates of merit may also be granted to physicians whose essays are rated second and third best. Contestants must be members of the American Medical Association who are residents of the United States. Five copies of each contribution, which should not exceed 5,000 words and which should be typewritten in English, should be in the hands of the secretary, Dr. Harold Swanberg, 209 W. C. U. Building, Quincy, Ill., not later than May 1, 1942. Further details may be secured from Dr. Swanberg.

## Book Reviews

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**Exercises in Electrocardiographic Interpretation.** By Louis N. Katz, M.D., Assistant Professor of Physiology, University of Chicago. Price, \$5. Pp. 222, with 189 electrocardiograms. Philadelphia: Lea and Febiger, 1941.

Experiments in methods of clinical teaching are always interesting. In 1906 Dr. Richard C. Cabot, of Boston, published a volume "Case Teaching in Medicine." It was an effort to apply to medicine the case-teaching method used successfully in the Harvard Law School. The teacher could obtain a key list of the correct diagnosis for each case reported, so that he was always sure to be right, and the students could struggle over the Cabot records to their hearts' content, acquiring considerable agility in that form of mental gymnastics which has to do with the clinical management of paper patients.

This particular method of teaching met with a certain degree of favor for a time and was applied to other fields—pediatrics, neurology and obstetrics. On the whole, however, while the clinical-pathologic conference has survived from it, the patient in vivo has seemed better to study than the patient in vitro, and clinical clerkships have proved infinitely more educational than even the most careful analysis of case histories.

"Exercises in Electrocardiographic Interpretation" is an outcropping of a tendency toward reviving this old teaching method and applying it to a new field. The book begins with a 17 page discussion of how to analyze, describe and interpret electrocardiograms. This is followed by 90 short case reports, each accompanied by beautifully reproduced electrocardiographic tracings pertinent to the case described, intelligently and skilfully interpreted. At the end three appendixes deal with ways of filing and classifying electrocardiograms in a systematic and approved fashion.

Such a method of teaching electrocardiographic interpretation may well prove helpful to many groups of physicians or students. This reviewer confesses to remembering with much pleasure a game of penny ante which for a time was fashionable in the hospital in which he resided. A group of interns would assemble, and each man would put up a penny for each tracing which the cardiologist would supply for the evening's entertainment. The intern who interpreted correctly any single tracing which the others missed would win all money placed on that particular tracing, but if half or more of the group interpreted the same tracing correctly, no pennies would change hands, such an occurrence being the foundation for building up a small jack pot. It was a good game while it lasted and besides being fun to play evolved into a useful method of instruction. Perhaps this book will help to resurrect that particular indoor sport.

**Essentials of Electrocardiography.** By Richard Ashman, Ph.D., and Edgar Hull, M.D. Price, \$5. Pp. 373, with 122 figures. New York: The Macmillan Company, 1941.

The first edition of "Essentials of Electrocardiography" appeared four years ago. As the authors point out, since that time there have been numerous accretions to the knowledge of cardiography; consequently, it has been necessary to rewrite a goodly part of the book and to increase its length. As a matter of fact, it might be said almost to be a new book, in contradistinction to a second edition in which a few minor changes have been made.

The book consists of 15 chapters, together with an appendix and an excellent bibliography, the latter some 20 pages long. The same general form is followed as was used in the first edition. The usual introductory chapters on the fundamentals of the electrocardiogram occupy a considerable portion of the book.



The reader, being familiarized with the basic principles and with the normal electrocardiogram, is then introduced to the abnormal deviations that appear as a result of heart disease, anemia, a metabolic disturbance, a toxic state, infection or any one of the host of conditions which may produce alterations from the norm.

The reviewer has nothing but praise for this book. The senior author is one of the pioneers in the study of the physiology of the heart by means of the electrocardiogram. The junior author is a skilled clinician and is apparently responsible for the clinical features, which are so well presented. The format is excellent; the subject matter is printed on a high grade, semiglossy paper which reproduces well the expected innumerable electrocardiograms. The book can be recommended highly to the tyro in this field, to the clinician who dabbles in electrocardiography and to the skilled electrocardiographer who may wish at times to consult a magnificent reference book and to obtain the opinion of others who are skilled in this field.

**An X-Ray Atlas of Silicosis.** By Arthur J. Amor, M.D. (Lond.), M.Sc. (Wales), Honorary Physician, Clydach Memorial Hospital; Medical Officer, Mond Nickel Co., Ltd., Swansea, Wales. With translation of the legends into French by Robert E. Horne, M.A. (Wales), Medical Secretary, Mond Nickel Co., Ltd., Swansea, Wales. Price, \$8, cloth. Pp. 206, with 72 illustrations. Baltimore: Williams & Wilkins Company, 1941.

Since so many of the general textbooks of medicine devote so little space to silicosis, this atlas should occupy a prominent place in the newer concept and the diagnosis of this industrial disease. The author has had many years of experience among the industrial workers of South Wales, including the medical supervision of a large colliery. He has kept accurate and careful records of thousands of cases and has verified the diagnoses by postmortem examinations and by the statutory certificates of the Silicosis and Asbestosis Medical Board.

The first portion of the book consists of 5 chapters devoted to the etiology, pathology, roentgenology, clinical manifestations and prognosis of silicosis. A brief discussion of the roentgen anatomy of the normal chest is included in this section. The division of silicosis into three clinical stages, as described by Sutherland and Bryson, is employed. Stages 1 and 2 each are subdivided further into three subtypes. The association of tuberculosis and silicosis is considered fully.

The atlas contains 72 excellent full page reproductions of roentgenograms which illustrate the various stages and types of silicosis as well as the most frequent complication, tuberculosis. In several instances, reproductions of photographs and roentgenograms of the lung made post mortem are included. On the page opposite each illustration are legends in English and French describing the occupation and a brief medical history of the patient, the roentgenographic findings and the diagnosis of his condition. A short bibliography is included.

**The Microbe's Challenge.** By Frederick Eberson. Price, \$3.50. Pp. 354. Lancaster, Pa.: The Jaques Cattell Press, 1941.

Under this intriguing title and covered by a dramatic dust wrapper is a really excellent book for the layman on bacteriology and infectious disease. An extract from the publisher's letter gives perhaps better than the reviewer can an outline of its substance:

"The book deals with one of the brightest chapters in medical history, telling a story of war against disease and the vaunted conquests of man over his invisible germ enemies. Against a historical background of past and present medical discoveries and their application is shown how microbes wage war against man with counter-attacks of their own, ingenious and diabolically human. The novelty of the theme is in its presentation from the point of view of a microbial 'struggle for existence' as they seek food, shelter and continuous survival at the expense of human and animal 'hosts,' leaving disease in their wake.

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"The author shows that in this changing world, microbes have been changing too, deriving their power from new characteristics in the body of a victim, or while passing from one to another. It tells of epidemics and what science does to prevent outbreaks of disease; how new diseases are created which later turn out to be new forms of the old. Man the conqueror finds himself outflanked by a smart adversary in the exciting chapters on the mysteries of infantile paralysis, yellow fever, malaria, influenza, plague and the various viruses—carriers of disease."

The author in the effort to catch the reader's fancy has titled his chapters with all sorts of vivid legends, such as "Virus Riddles," "Jekyll and Hyde Types," etc., but when one comes to "The Taming of the Flu" one feels (as P. G. Wodehouse would say) that this is a shade over the odds.

**The Principal Nervous Pathways.** By A. T. Rasmussen, Ph.D., Professor of Neurology, Department of Anatomy, University of Minnesota Medical School. Second edition. Price, \$2.50. Pp. IX + 73, with 28 illustrations. New York: The Macmillan Company, 1941.

The first edition of this book appeared in 1932. For some reason it was not much noticed by the ordinary clinician, though it was reviewed favorably by such special journals in the field of neurology as the *Archives of Neurology and Psychiatry* (27:1513 [June] 1932) and the *Journal of Nervous and Mental Disease* (76:94 [July] 1932).

Now that internists wish to have at least a bowing acquaintance with the central nervous system this recent edition is a godsend, for it is as simple a book on so complicated a subject as there can be, pretending to be no more than a finely reproduced graphic presentation of the chief nervous pathways.

The second edition is the same size as the first, but the author has made such alterations in text and illustrations as to bring out changes which have become reasonably well established as new knowledge in the past decade. Thus here is a means of teaching pictorially to any interested students the essentials of modern neuroanatomy.

The author admits that some of the cuts may seem to be overburdened with legends. On the other hand, most readers will agree that this is better than to be forced to hunt up some other sketch in order to find the name of a structure that is shown but not labeled.

The book is a useful tool for students or for the harassed internist who wishes to learn the precise anatomic sites of many physical changes which are readily demonstrable at the bedside. It deserves great success.

**Essentials of Endocrinology.** By Arthur Grollman, Ph.D., M.D., Associate Professor of Pharmacology and Experimental Therapeutics (formerly Associate Professor of Physiology and Instructor in Chemistry) in the Johns Hopkins University School of Medicine. Cloth. Price, \$6. Pp. 480, with illustrations and index. Philadelphia: J. B. Lippincott Company, 1941.

Should the reviewer be asked to choose a single volume book about the hormones for the student or the practitioner of medicine, he would unhesitatingly recommend this one. The author has presented a "critical evaluation of all important aspects of the subject." To quote further from the preface, "Clinical endocrinology is frequently befuddled by accepting unproved assumptions as basic facts and building upon the insecure foundations, thus established, a maze of fanciful and ill-founded conjectures. When reduced to its experimentally established facts, clinical endocrinology can be placed on a scientifically sound basis. Since so much of endocrinology is based on observations in human disease, it is impossible to dissociate experimental from clinical endocrinology."

The exposition is sane and cautious as well as orderly. In each instance the fundamental facts of gross, comparative and microscopic anatomy, embryology, physiology and pathology on which the experimental and the clinical studies are based are stated and discussed. No conclusion is drawn unless it is fully supported

both by clinical and by experimental evidence. The illustrations and charts are excellent and clear. A carefully selected but adequate bibliography is inserted at the end of each chapter.

**Therapeutisches Taschenbuch.** By P. Mühlens, M.D., Director of the Institute for Tropical Disease, Hamburg, Germany. Second edition. Price, 1.50 marks. Pp. 76, with 20 illustrations. Leipzig: Georg Thieme, 1941.

The first edition of this booklet came out in 1939. *The Journal of the American Medical Association* acknowledged its appearance (114:917 [March 9] 1940) and seemed somewhat scandalized by its short skirts. *The Journal* termed the little volume too brief and sketchy and suggested that here was an attempt at oversimplification of a serious subject. Evidently this hussy had more appeal than was strictly commendable in the society of good medical books, however, for the author says that the first edition of 2,000 copies was gobbled up within a year of its printing.

The second edition has now been published, and no doubt the book will once again captivate many readers with its brusqueness of style and its abbreviated costume. It pretends to do no more than give a bird's-eye view of the most common tropical diseases and their treatment. The serious student of tropical medicine can properly object to the book's superficiality. Many readers, however, will like to know of its existence and that here can be found an extremely condensed account of the kind of medical problem with which an expert in the field of tropical medicine is now forced to contend.

**Shock Treatment in Psychiatry: A Manual.** By L. Jessner, M.D., and V. Gerard Ryan, M.D. Price, \$3.50. Pp. XV + 149. New York: Grune and Stratton, Inc., 1941.

This short monograph reviews in a workman-like manner the use of insulin, metrazol and electricity as agents for inducing convulsing shocks in psychiatric therapy. These three agents and the technics of their usage are evaluated critically and in language that any one can understand.

Each chapter is built on the same lines. A short historical account is followed by a description of technical procedures, a statement of the indications and the contraindications for using the agent under discussion and, finally, a general summary of the results to be expected. As a concluding chapter, the author supplies a bibliography of 353 references culled from several thousand titles.

The book begins with an introduction by Dr. Harry Solomon. He says that it is an excellent handbook; and so it appears to be, useful not only to the psychiatrist but to the internist, who nowadays, perforce, is supposed to be somewhat informed about the problems of shock therapy, and to the inquiring medical student. On the whole, this unassuming small volume deserves high praise.

## CALCIFICATION OF THE PANCREAS

ARTHUR B. KING, M.D.

AND

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BALTIMORE

Deposition of calcium salts in the pancreatic tissue is an uncommon pathologic finding. Clinical diagnosis of the condition is even more unusual, and few case histories have been reported. Beling,<sup>1</sup> in a thorough survey of the literature, found 12 cases in which diffuse calcification of the pancreas was thought to be present, and to these he added an instance of his own. We have reviewed the original articles and cannot agree that cases 1 and 3 cited by him have sufficient evidence to be considered examples of the syndrome under discussion.

According to Mayo,<sup>2</sup> two types of calcium deposits within the pancreas have been described. The first, "true stones," are concretions of calcium salts lying free in the ducts. These may be single or multiple and usually lie in the larger ducts. The second variety he termed "false stones," actual calcifications of the parenchyma of the pancreas. It is the latter condition which will be considered. True stones, which sometimes occur in conjunction with the calcareous precipitations in the gland, are apparently not essential to the latter condition.

Including the case presented by Beling but excluding cases 1 and 3 in the résumé compiled by him, there are, we believe, 11 recorded instances in which clinical, roentgenologic and pathologic data are sufficient to warrant the diagnosis of calcification of the pancreas. For a more extensive review of the literature, the article of Beling should be consulted.

We wish to record 3 examples of this condition observed by one of us and also give a brief summary of a case which may fit into this category.

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From the Subdepartment of Neurology of the Johns Hopkins University School of Medicine and the Department of Medicine of the Baltimore City Hospitals.

1. Beling, C. A.: Calcification of the Pancreas, *Am. J. Digest. Dis.* **7**:231, 1940.

2. Mayo, J. G.: Pancreatic Calculi, *Proc. Staff Meet., Mayo Clin.* **11**:456, 1936.

## REPORT OF CASES

CASE 1.—P. D., a white man aged 35, came to the Johns Hopkins Hospital complaining of abdominal pain of six weeks' duration. The family history was noncontributory. As a child he had had mumps, complicated by orchitis on the left side. Three years before his entrance into the hospital an appendectomy had been performed. For a long period he had been a heavy drinker, and the year following the operation, while he was undergoing a cure for alcoholism at a local hospital, glycosuria was discovered. The diabetes was controlled by diet, but after leaving the hospital he had returned to his former habit and sugar reappeared in the urine. During rehospitalization, diabetes was controlled by a daily dose of 45 units of insulin. At the time of discharge the urine was kept sugar free by diet alone.

Six weeks before admission to the Johns Hopkins Hospital the patient experienced a dull ache in the epigastrium, most severe in the afternoon and evening. Ingestion of food increased the discomfort, and sodium bicarbonate did not afford relief. Ten days previous to entrance a sudden attack of vomiting occurred, and the vomitus contained all he had eaten for the past two days. He recognized undigested food particles, but neither blood nor pus was noted. He was admitted again to a local hospital, where the epigastric pain became sharper and more severe but did not radiate. Ingestion of alcohol brought rapid relief. For two days no solid food was eaten because of the increased pain following meals. No history of jaundice, hematemesis, diarrhea, chills or fever could be obtained. Laboratory examination yielded the following salient data: a blood sugar value of 212 mg. per hundred cubic centimeters, glycosuria and radiopaque material in the upper part of the abdomen. The patient was referred to Dr. John T. Howard, of the Johns Hopkins Hospital, for further study.

Physical examination on admission to this hospital revealed nothing abnormal except the abdominal symptoms. The abdomen was symmetric and soft, with a well healed incision in the right lower quadrant. The edge of the liver could be felt 2 cm. below the right costal margin and was rounded and tender on palpation. Mild tenderness was elicited on deep pressure in the right upper quadrant near the midline of the abdomen.

Laboratory examination added the following information: red cell count, 5,310,000 and white cell count, 21,750 per cubic millimeter; hemoglobin content, 16.2 Gm. per hundred cubic centimeters, and corrected sedimentation rate 26 mm. at the end of one hour. A differential count of the white cells showed 6 per cent juvenile granulocytes, 74 per cent segmented neutrophils, 17 per cent lymphocytes and 3 per cent monocytes. Platelets were normal both in size and in quantity. The Wassermann reaction of the blood was negative. Determinations of the nonprotein nitrogen, sugar, calcium and phosphorus of the blood yielded values of 38, 210, 9.5 and 4.4 mg., respectively, per hundred cubic centimeters. The bromsulphalein test of hepatic function revealed less than 5 per cent retention. The urine was clear, with an acid reaction, a specific gravity of 1.032 and a positive reaction for sugar but with no albumin, acetone or cellular structures. Stools were of normal consistency but had a strongly positive guaiac reaction. They were also positive for fats and fatty acids, as demonstrated by the use of sudan III.

A dextrose tolerance test showed a high rise and slow fall of the blood sugar level (fig. 1), and specimens of urine consistently contained sugar. A normal flow of bile was found on duodenal drainage, but on microscopic examination of the fluid flocculi and many pus cells were seen. Tests for pancreatic enzyme activity failed to show any active trypsin or diastase. However, a twenty-four hour specimen of urine contained more than 1,200 units of diastase.

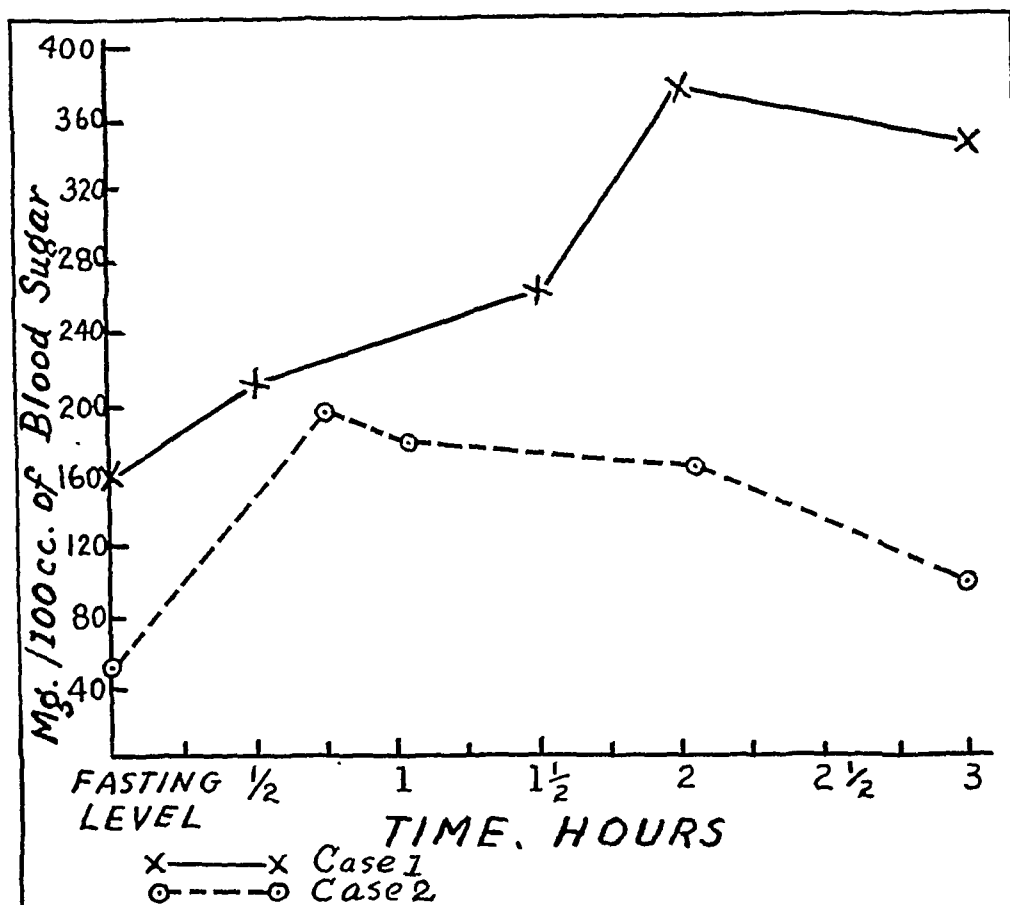


Fig. 1.—Dextrose tolerance curves in cases 1 and 2.



Fig. 2 (case 1).—Calcified particles outlining the pancreas.

Roentgen ray examinations revealed a normal heart and aorta, clear lungs, a normally functioning gallbladder in which no stones could be demonstrated and diffuse calcification of the entire pancreas (fig. 2).

With routine hospital care, the abdominal discomfort was almost entirely relieved. The diabetes was regulated, and the patient was discharged, having only to follow a prescribed diet to prevent glycosuria.

Four days after discharge the patient had a sudden, severe attack of pain in the upper portion of the abdomen, which lasted for several hours and was followed by frequent attacks of vague epigastric discomfort. He was readmitted five days later, at which time the physical examination disclosed nothing abnormal. The urine again contained sugar. The diabetes was quickly controlled by a 2,200 calory diet and 23 units of insulin daily. Ten days later an exploratory laparotomy was performed by Dr. W. F. Rienhoff Jr., who found the pancreas sausage shaped, freely movable, hard and dense, with the surrounding blood vessels small. The midportion of the gland was incised, and a small calculus fell out. The parenchyma was white and glistening, and no blood appeared on the cut surfaces. The ducts were probed in both directions and found patent. Disease of the biliary or the gastrointestinal tract was not evident. A portion of the pancreas was removed for microscopic study.

According to the report, the pancreatic tissue was scarce. There were a few acini, surrounded by large amounts of connective tissue, a few atrophic and scarred islands of Langerhans and several dilated ducts. Neither free calculi nor actual calcification was demonstrable.

After an uneventful postoperative course, the patient was discharged; his diabetes was under control, but the epigastric discomfort remained.

A third admission occurred five months later. Since the last discharge there had been occasional attacks of abdominal pain, which were relieved by morphine. The pain radiated to the right and left costal margins and to the lower left part of the chest. The results of physical examination were again essentially negative. Stools no longer showed free fat, and duodenal drainage yielded dark bile, which was normal microscopically. Free fat could be demonstrated in the duodenal contents by the sudan III stain. Active trypsin and diastase were absent. The diabetes was controlled by diet and daily administration of 20 units of protamine insulin.

Since the last admission, the patient has been seen frequently by his local physician. The abdominal pain continues but has diminished. Since his recent marriage his health is much improved.<sup>3</sup>

CASE 2.—A Negress aged 35 was admitted to the Baltimore City Hospitals with a complaint of pain in the right side of her abdomen. The family history was noncontributory. She had had the usual childhood diseases and had not undergone any operations. Three pregnancies had all terminated in miscarriage. Four years before admission she had been thrown from a motorcycle and had sustained fractures of the skull, ribs and right arm. For many years she has been a heavy consumer of beer and strong liquor. During the past year her weight had fallen from her average of 112 to 80 pounds (50.8 to 36.3 Kg.). Chronic constipation had been troublesome for many years.

The patient stated that for the past six months she had had periods of ill health characterized by pain in the lower right portion of the chest. Vomiting had been frequently associated with these attacks of pain. The pain and vomiting bore no relation either to the type of food eaten or to the time of ingestion.

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3. Crawford, R. H.: Personal communication to the authors.

For the past two months there had been an almost constant aching pain which included the entire anterior aspect of the right side of the chest and radiated through the scapula. Five days before admission the pain became severe and localized beneath the right costal margin.

Physical examination disclosed a small but well developed Negress who was not in acute distress. The skin showed evidence of loss in weight but was otherwise normal. Several observers mentioned slight tenderness in the right upper quadrant of the abdomen. However, no viscera or abdominal masses were palpated. Nothing further of importance was detected.

Laboratory procedures, which included complete studies of the blood, urine, stool and cerebrospinal fluid, disclosed nothing abnormal. The Wassermann reactions of the blood and spinal fluid were negative. Analysis of a fasting specimen of gastric contents showed 8 degrees of free and 12 degrees of combined hydrochloric acid. Visualization of the gallbladder, both after oral and after intravenous administration of radiopaque dye, showed a normally functioning organ with no evidence of stones. Visualization of the gastrointestinal tract demonstrated an irregularity in the prepyloric region of the lesser curvature of the stomach and failure of the duodenal cap to fill. This was interpreted as spasm; so the procedure was repeated, and it was decided that the upper part of the gastrointestinal tract was normal. Some abnormal calcification was present in the upper portion of the abdomen, but this was not commented on.

Soon after admission the pain disappeared and the appetite returned. A low grade fever, never satisfactorily explained, persisted throughout the stay in the hospital. Eructation was frequent after meals, but there was no complaint of discomfort. On discharge, a diagnosis of possible cholecystitis was made.

After remaining well for approximately eighteen months, she experienced, on May 27, 1938, severe, sharp substernal pain, which subsided after a short rest in bed. Discomfort returned the following day, and the patient remained in bed until her second admission to the Baltimore City Hospitals, on June 3. Three days after the onset of abdominal pain, intermittent attacks of vomiting appeared, and both pain and vomiting persisted until her arrival at the hospital. On one occasion blood was noted in the vomitus.

On admission, the temperature, pulse and respiration were normal; the blood pressure was 110 systolic and 80 diastolic, and the results of physical examination were entirely negative. Laboratory studies, however, showed many changes since the previous admission. Examination of the urine and blood revealed nothing abnormal. The reaction to 0.1 cc. of old tuberculin in a dilution of 1:1,000 was positive. The Wassermann reaction of the blood was positive, but that of the cerebrospinal fluid was negative. Blood sugar estimations showed 98 and 87 mg. per hundred cubic centimeters (fasting specimens). The concentrations of calcium and phosphate were 8.8 and 4.0 mg., respectively, per hundred cubic centimeters of blood. Analysis of gastric contents during fasting showed no free but 12 degrees of combined hydrochloric acid; after administration of alcohol, 32 degrees free and 18 degrees combined acid, and after injection of histamine, 35 degrees free and 55 degrees combined acid. A dextrose tolerance test gave a curve with a steep rise and a slow fall (fig. 1). Specimens of urine collected during the test showed values for sugar varying from 0.2 to 0.5 mg. per hundred cubic centimeters.

The stools were not grossly abnormal, but fecal material stained with sudan III disclosed a marked increase of fat. There was no amylase in the stools, and



only traces were present in the urine. The tests were repeated one month later, with similar results. Analysis of the duodenal contents, obtained by direct drainage, disclosed 3 units of amylase (normal, 40 units) but no trypsin. These tests were repeated, with the same results.

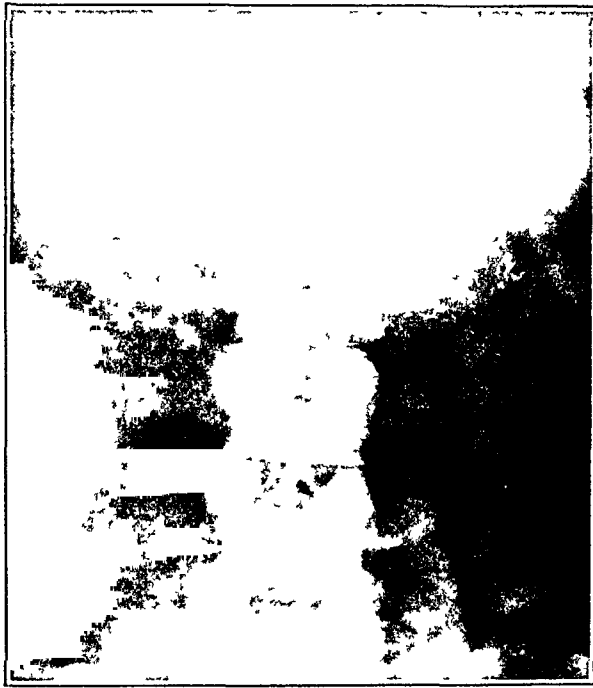


Fig. 3 (case 2).—Calcification in the upper part of the abdomen in the region of the pancreas

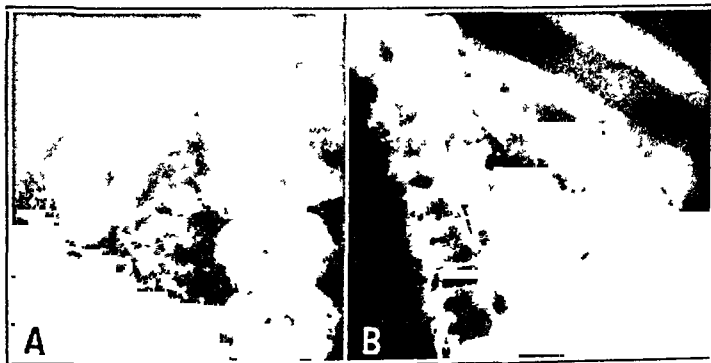


Fig. 4 (case 2).—*A*, anteroposterior view of the calcification in the region of the pancreas shown in relation to the gallbladder, which is filled with radiopaque dye. *B*, lateral view taken at the same time.

Roentgenograms of the chest, gallbladder and gastrointestinal tract were normal. Plain roentgenograms of the abdomen taken at this time showed many radiopaque bodies in the region of the pancreas which were interpreted as calcification of the pancreas (figs. 3 and 4).

The patient's discomfort rapidly disappeared when she was given a high carbohydrate, low fat diet, and she was discharged without further treatment.

CASE 3.—E. B., a Negress aged 17, was admitted to the Baltimore City Hospitals on June 3, 1937 because of polyuria. The family history is of interest because of the prevalence of obesity. The mother weighed 185 pounds (83.9 Kg.) at the age of 18 years, and at the time of admission the patient weighed 246 pounds (111.6 Kg.). A sister aged 13 weighed 186 pounds (84.4 Kg.) and the father 175 pounds (79.4 Kg.). The patient stated that as a child she had had measles, pertussis, diphtheria, scarlet fever and pneumonia. Since then she had suffered from frequent colds and sore throats. Menstruation had started at the age of 11 and had since been irregular. Periods lasted four days, during which considerable flow was present and often severe, cramping pain.

The illness which brought her to the hospital consisted only of moderately severe polyuria (1.5 to 7 liters in twenty-four hours) and a slight loss of weight. The duration of the symptoms was not stated. On admission, the general physical examination revealed nothing abnormal except marked obesity. Urinalysis revealed glycosuria (4 plus) and acetone (1 plus) but no diacetic acid. Determination of the sugar and cholesterol content and of the carbon dioxide-combining power of the blood yielded values of 480 mg. and 150 mg. per hundred cubic centimeters and 47.5 volumes per cent, respectively.

The diabetes was easily regulated and the patient was placed on a daily maintenance dose of 20-0-20 units of regular insulin. While she was in the hospital, the Wassermann reaction of the blood was positive and the basal metabolic rate was +24 per cent. A roentgenogram of the skull showed no abnormalities of the sella turcica.

After discharge, the patient remained well until July 11, 1939, when she was readmitted because of pyelitis. The infection of the urinary tract subsided quickly under conservative therapy, and the diabetes was again regulated on the same dose of insulin. She was discharged after a short stay.

On August 20 the patient had a sudden chill, followed by malaise and pain in the left side of the abdomen. The next day she became nauseated, vomited and ate nothing. These symptoms persisted; so she did not take her insulin. She was readmitted on August 23.

At the time of examination the patient was not in acute distress. The temperature was 105 F., the pulse rate 130 beats per minute, the respiratory rate 28 per minute and the blood pressure 150 systolic and 80 diastolic. The skin was hot and dry, and there were numerous striae over the upper extremities and abdomen. Moderate spasm and tenderness were present in the left lower quadrant of the abdomen. Otherwise, the physical examination revealed nothing abnormal.

The urine contained albumin (1 plus), sugar (4 plus), acetone (3 plus) and large numbers of white blood cells but no red cells or casts. Examination of the blood showed 3,550,000 red cells and 19,300 white cells per cubic millimeter and 11 Gm. of hemoglobin per hundred cubic centimeters of whole blood. The blood contained 572 mg. of sugar, 26 mg. of nonprotein nitrogen and 26 mg. of cholesterol per hundred cubic centimeters, and the carbon dioxide-combining power was 25 volumes per cent. The serologic reaction of the blood for syphilis was positive, but that of the spinal fluid was negative. No abnormalities of the stools were noted.

The diabetic acidosis was treated vigorously, and sulfanilamide was given for the infection of the urinary tract. Five days later the temperature had fallen to normal, but severe secondary anemia had developed. The sulfanilamide was discontinued, and ammonium mandelate was administered for ten days. By this time the pyelitis had subsided and the diabetes was controlled.

Roentgenograms of the chest, together with intravenous and retrograde pyelograms, failed to reveal any abnormality of the kidneys (fig. 5). Plain roentgenograms of the abdomen revealed many small calcified areas in the epigastrium, which were interpreted as calcification of the pancreas. Unfortunately, no determinations of the activity of the pancreatic enzymes were carried out.

The following case history was discovered in the files of the department of pathology of the Johns Hopkins Hospital. The clinical records



Fig. 5 (case 3).—Calcification in the pancreas shown in relation to the renal pelves, which are demonstrated by means of an intravenous pyelogram.

are scanty, and as the patient died in 1891, roentgenograms and enzyme studies are lacking. The pathologic findings are so typical, however, that we feel certain the case is one of false pancreatic stones.

CASE 4.—H. W., a white man aged 43, was admitted to the medical service of the Johns Hopkins Hospital on Oct. 2, 1890 with a complaint of jaundice. The family history was noncontributory. For many years he had been a heavy drinker of strong liquor. Five years before there had been an episode of chills and fever, the duration of which was not stated. An attack of pain in the abdomen, with generalized soreness of the back lasting for several days, had occurred one year before entrance to the hospital. Six months after this there had been frequent attacks of vomiting. About one week before admission epigastric pain, which radiated through to the back, had been experienced, and jaundice had appeared shortly afterward. The latter had already begun to subside, and the abdominal discomfort had disappeared at the time he was seen by physicians at the hospital.

Physical examination revealed nothing abnormal except slight jaundice. No abnormalities of the urine were recorded. The icterus subsided rapidly, and the patient was discharged nine days later, with the diagnosis of catarrhal jaundice.

*Pertinent Data in Four Cases of Calcification of the Pancreas*

	Case 1	Case 2	Case 3	Case 4
Alcoholism.....	Chronic	Chronic	Absent	Chronic
Pain				
Duration.....	6 weeks	5 days; 6 days 18 mo. later	None	5 yr.; 1 yr.; in- definite periods
Location.....	Epigastrium	Right costal margin	None	Epigastrium
Radiation.....	Right and left costal margins and lower left chest	Right side of chest anteriorly through to scapula and under sternum	None	Through to back
Increased by taking food	Yes	No	—	—
Increased by type of food	No	No	—	—
Fever.....	Present for in- definite period	Present for in- definite period	Present for in- definite period	Present for in- definite period
Chills.....	None	None	Present	Present
Nausea.....	Present	Present	None	Present
Vomiting.....	Present	Present	None	Present
Jaundice.....	None	None	None	Marked 5 years before; slight on admission
Diarrhea.....	None	?	None	None
Concomitant disease...	None	Motorcycle accident	Pyelitis; glan- dular deficiency (?)	Tuberculosis
Tenderness at the time of physical examina- tion	Epigastrium and right upper quad- rant of abdomen	None	None	None
Fever during hospitali- zation	None	None	None	None
Laboratory findings				
Red cell count.....	Normal	Normal	Normal	?
White cell count.....	21,750	Normal	19,300	?
Sedimentation rate...	26 mm. per hr.	Normal	?	?
Urine				
Sugar.....	Present	None	Present	None
Amylase.....	1,200 units	None	?	?
Other substances...	None	None	Acetone, albu- min, white cells	None
Stool				
Gross appearance..	Normal	Normal	Normal	Normal
Fat (sudan III)....	Present	Present	None	?
Trypsin.....	None	3 units	?	?
Amylase.....	None	None	?	?
Duodenal drainage				
Amylase.....	0 units	3 units	?	?
Trypsin.....	0 units	0 units	?	?
Gallbladder				
Roentgenogram....	Normal	Normal	Normal	—
Operation.....	Normal	—	—	Normal (autopsy)
Appearance of pancreas	Hard, white, scarred	—	—	Hard, white, scarred, cal- cium deposits
History of loss of weight	None	32 pounds (14.5 Kg.)	Moderate	Marked

He reappeared in the outpatient department on July 29, 1891, with the complaint of cough and dyspnea of one week's duration. Hospitalization was advised, and on entry into the ward his temperature was 102.4 F., his pulse rate 128 per minute

and his respiratory rate 36 per minute. Physical examination showed yellow-tinged scleras. There were signs of a pleural effusion on the right side of the chest, and tubercle bacilli were present in the sputum. The patient rapidly became worse and died five days after admission.

At autopsy a widely dilated pancreatic duct containing many calculi was found. The pancreas was hard and atrophic. When the gland was cut, it imparted a gritty sensation, and deposits of calcium salts were found throughout the parenchyma. No microscopic sections were made. Examination of the lungs disclosed advanced tuberculosis.

#### COMMENT

Haggard and Kirtly<sup>4</sup> found reports in the literature of 204 cases in which the diagnosis of pancreatic lithiasis had been made. Included with these are the 12 cases of calcification of pancreatic tissue cited by Beling. The incidence of pancreolithiasis observed post mortem is cited by several authors as varying from 1 case in 1,500 to 1 case in 2,500 consecutive autopsies. We have found 5 instances in the first 16,000 autopsies performed at the Johns Hopkins Hospital and none in the first 8,000 done at the Baltimore City Hospitals. Of the 209 cases now recorded, actual calcification of the gland occurred in only 15 (7.1 per cent). In 6 cases the patient was operated on or was examined post mortem, and in every instance true pancreatic stones were found, in addition to the diffuse calcification.

The cause of the calcification is obscure. Mayo expressed the belief that it is due to pancreatitis, in turn produced by chronic disease of the biliary tract. This was refuted by Haggard and Kirtly,<sup>4</sup> who pointed out that gallstones were found in only 9 of the 65 cases of pancreolithiasis in which there was surgical intervention. Biliary calculi were not demonstrated in any of our cases.

A history of signs and symptoms suggestive of cholecystitis is more frequently elicited, being present in 3 of our patients. However, pain severe enough to be interpreted as biliary colic is rare. Should pancreatitis due to infection of the biliary tract precede the calcification, it probably is chronic, slowly progressing cellulitis rather than the severe generalized reaction that follows obstruction of the ampulla of Vater by a biliary calculus, causing an influx of bile into the pancreatic passages.

The length of time between the onset of the postulated pancreatitis and the appearance of the calcification is not known. Patients are often first seen many years after the initiation of symptoms, and when the calcified areas are discovered in roentgenograms, there is no way of determining how long they have been present. There is some evidence that the deposition may be rapid. Chiray, Albot and Bolgert<sup>5</sup> found

4. Haggard, W. D., and Kirtly, J. A.: Pancreatic Calculi, *Ann. Surg.* **109**:809, 1939.

5. Chiray, M.; Albot, G., and Bolgert, M.: Etude clinique et biologique d'un cas de lithiase généralisée du pancréas, *Ann. méd.* **38**:348, 1935.

larger quantities of amylase and trypsin in the duodenal contents after one year's observation of their patient. This led them to the conclusion that some regeneration had occurred and that the inflammation had subsided. The pancreas may have sustained a rapid widespread destructive process followed by calcification, but with slow hypertrophy of the surviving tissue. We know that the roentgenogram may show a marked increase in the amount of calcium deposited within eighteen months. In case 2 of our series the first examination was made in January 1937, and only a few calcified areas are apparent in the roentgenograms of the abdomen taken at that time, but in those taken in May 1938 the typical picture of generalized calcification is present. During the interval there were no symptoms of an inflammatory process.

Chronic alcoholism has been mentioned in many cases, and in 3 of our cases the patients were consumers of large quantities of alcohol. However, the patient in case 3 of our series was a young girl who, as far as we know, never drank alcoholic liquors. The role of alcoholism, beyond its apparent frequency, is not known at this time. Certainly, it is not the sole agent in producing the calcium deposits in the pancreas.

Tuberculosis is rarely responsible for calcified areas in the pancreas. Even extensive generalized tuberculosis seldom involves this gland. We consider its presence in case 4 incidental. The same may be said for syphilis and other chronic diseases. One of the acute infectious processes that might be implicated is mumps, which may cause pancreatitis (case 1). Neither in our cases nor in those reported in the literature was there any evidence that the calcium metabolism was abnormal or that a generalized calcium-depositing dyscrasia was present.

The symptomatology is not at all characteristic, the most constant complaint being a poorly localized pain in the upper part of the abdomen. There may be no physical signs. Clinical diagnosis is made on roentgenographic findings alone, as the deposits of the calcium salts are radiopaque. The gland is outlined so clearly that there can be little doubt as to the location of the calcification.

Carbohydrate metabolism is commonly deranged, and Mayo stated that diabetes is frequent. Oser (cited by Chiray and associates) found glycosuria in 24 of 70 cases of pancreatic lithiasis. Glycosuria is mentioned only once in the 11 cases of diffuse calcification of the pancreas reviewed by Beling and checked by us, while an abnormal dextrose tolerance curve was noted in another. Two of our patients had diabetes, while the blood sugar curve of a third was distinctly abnormal (fig. 1). We feel that disturbances of carbohydrate regulation are probably frequent and would be reported more often if dextrose tolerance tests were routine.

Because of our ignorance of the cause and the extensive involvement of the pancreas, no satisfactory method of treatment has been decided on.

Study of the pancreatic enzymes in the urine led to the conclusion that the pancreatic duct was occluded in 1 of our patients, and therefore an exploratory laparotomy was performed, but the main duct was patent. Two patients became asymptomatic under supportive care, and we felt that surgical intervention was not indicated. However, we are by no means satisfied that all types of treatment are unnecessary, and if there is any evidence of a pancreatic abscess or cyst, the lesion should be searched for and treated by the usual surgical methods. A high carbohydrate diet seemed beneficent for 1 of our patients.

Prognosis for the condition is good, but there may be recurrent attacks of pain of varying frequency for many years. Diabetes is not common, but when present is usually mild, shows little tendency to progress in severity and is easily controlled by small amounts of insulin.

#### SUMMARY

A review of the literature has disclosed accounts of 11 cases of diffuse calcification of the pancreas. Records of 4 additional cases have been presented and the salient facts summarized in a table. The cause, diagnosis, treatment and prognosis have been discussed.

Dr. John T. Howard, of the Johns Hopkins Hospital, and Dr. R. H. Crawford, of Rutherfordton, N. C., permitted us to report case 1.

# RELATION OF CALCIUM AND LIPIDS TO ACUTE PANCREATIC NECROSIS

REPORT OF FIFTEEN CASES, IN ONE OF WHICH  
FAT EMBOLISM OCCURRED

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AND

IRVING A. FIELDS, M.D.

LOS ANGELES

Many facts concerning acute pancreatic necrosis and the accompanying pathophysiologic changes have been well known for years. The yellow-white areas of "fat necrosis" in and around the pancreas were so named by Balser.<sup>1</sup> Langerhans<sup>2</sup> described the action of lipase in splitting neutral fat into fatty acid and glycerin, the latter being absorbed and the fatty acid deposited as needle-like crystals, which combine with calcium to form soaps. Frugoni and Stradiotti<sup>3</sup> stated that 85 per cent of the soaps so formed may be insoluble.

Probably in no other disease is there such sudden demand for calcium, the amount needed depending on the extent of fat necrosis and the subsequent liberation of fatty acids.

We have been unable to find records of further investigations of the rôle of calcium in this disease, either as to the amount combined with the fatty acids in situ or as to the effect of the disease on serum calcium values. The present paper is based on studies of the latter aspect.

Serum lipid determinations were made in some cases, in a search for indications of absorption of neutral fat into the blood (the method used includes determination of fatty acids<sup>4</sup>). It is possible that both neutral fat and fatty acids, such as oleic acid, which is liquid at body temperature, might find their way from the necrotic tissue into the blood stream. Neutral fat is also a solvent for fatty acids, even after they have

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This study was aided by a gift from Ethel Mossman Jacobs.

From the Department of Pathology, University of Southern California School of Medicine, and the Laboratory, Los Angeles County Hospital.

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combined with calcium to form soaps, and thus the acids if absorbed may carry soaps with them.

A few clinical and experimental observations have been made on the lipids in the blood. Wiesel<sup>5</sup> noted fat in the vessels of the liver at necropsy in 3 instances. In 2 of these fat was also present in the renal vessels. The pulmonary vessels were not mentioned. Wijnhausen<sup>6</sup> observed hypercholesterolemia and xanthomatosis of the skin in a 35 year old man with diabetes. At operation chronic pancreatitis and a few areas of fat necrosis were seen. No attacks of typical acute pancreatitis had been noted clinically. Joel<sup>7</sup> studied the blood serum of a young girl in whom acute pancreatic necrosis was observed during a surgical exploration. The serum was grossly milky. The content of cholesterol in the blood was 360 mg. per hundred cubic centimeters, and the amount of neutral fat was estimated at ten times normal, not enough serum being available for actual quantitative determination. Five days later the level of cholesterol was 150 mg. per hundred cubic centimeters, and there was no visible evidence of an increase in serum lipids.

Binet, Brocq and Ungar<sup>8</sup> produced experimental pancreatitis in dogs and observed an increase both in serum cholesterol and in the total lipids. They reported values for serum cholesterol as high as 840 mg. per hundred cubic centimeters and values for total lipids as high as 740 mg. Total lipids were not determined for the dog with a cholesterol value of 840 mg. per hundred cubic centimeters. The authors called attention to a patient with fatal acute pancreatic necrosis for whom the values for total lipids and serum cholesterol were 2,880 and 604 mg. per hundred cubic centimeters, respectively. Brunner<sup>9</sup> reported the results of serum cholesterol and fatty acid determinations for 4 persons with acute pancreatic necrosis. The fatty acids were estimated by Bloor's<sup>10</sup> method, which includes determination of neutral fat. For 1 patient the value for fatty acids was 3,440 mg. per hundred cubic centimeters, the normal being 350 mg. The value for serum cholesterol was 1,040 mg. per hundred cubic centimeters. Fatty acids

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ranged from 368 to 575 mg. and cholesterol from 127 to 264 mg. in the remaining 3 patients.

Our attention was first called to this subject by the condition of a patient who was found to have fat embolism and whose chief symptoms were shock and tetany.

REPORT OF THE CASE OF ACUTE PANCREATIC NECROSIS  
WITH ASSOCIATED FAT EMBOLISM

F. H. (case 4 of table 2), a 48 year old Mexican woman, entered the Los Angeles County Hospital on Dec. 30, 1939. According to her history, two weeks before entry she had had feverish sensations, nausea and vomiting. Apparently she had recovered, but twenty hours before entry she had had an attack of severe epigastric pain and repeated vomiting. When she was admitted to the hospital, she appeared to be in severe shock; the radial pulse could not be felt, and the oral temperature was 97 F. Typical carpopedal spasm was present, but neither Chvostek's nor Trousseau's sign could be elicited. A mass could be felt in the upper part of the abdomen. The carbon dioxide-combining power of the plasma was 47 volumes per cent. The leukocyte count was 9,100, with 72 per cent neutrophils. The urine contained albumin (2 plus) and many hyaline casts. The level of urinary diastase was within the normal range. The patient's condition rapidly became more serious, and she died nine hours after entry.

*Necropsy.*—The body was that of a well nourished woman, measuring 160 cm. in length and weighing 63.5 Kg. The feet and hands were flexed. The abdominal cavity contained 200 cc. of cloudy fluid. The tissues about the pancreas, including the mesocolon, were yellowish brown and necrotic. The foramen of Winslow was completely closed. The lesser peritoneal cavity was obliterated by hemorrhage and by swollen, friable, discolored tissue, masses of which broke away readily on manipulation. Necrotic yellow-white areas alternated with islands of hemorrhage throughout the interstitial tissue of the pancreas and in the peripancreatic tissue, extending as far as the upper pole of the left kidney and to the left half of the diaphragm. In the central portion of the pancreas some of the glandular tissue appeared to be fairly normal. The duct of Wirsung contained some clear secretion. Many small veins in and around the pancreas were filled with antemortem clots.

Many adhesions were present around the thickened wall of the gallbladder, which contained about forty black faceted calculi, measuring 5 to 6 mm. in their greatest dimensions. The common duct had a maximum circumference of 1 cm. The common duct and the duct of Wirsung opened side by side in a normal arrangement. The pleural surfaces were smooth. The right lung weighed 380 Gm. The lower lobe was partially collapsed, and dark blue-red areas were seen beneath the pleura. On section blotchy, dark red atelectatic areas interspersed with gray air-containing tissue were seen throughout the lobe. The left lung weighed 360 Gm., and its appearance was similar to that of the right. The consistency of the kidneys was less firm than normal. No gross changes were evident in the heart. The brain was not examined.

The blood was of a peculiar plum color, quite different from that ordinarily seen at autopsy. Blood with a similar color has been observed by one of us (H. A. E.) in a person with severe hyperlipemia (8,400 mg. of lipids per hundred cubic centimeters of blood).

*Microscopic Observations.*—In the pancreas there was extensive necrosis of the interstitial tissue, ducts and acini at the periphery of the lobules. Many acini and some small ducts appeared to be normal. Wide areas of necrosis extended into the peripancreatic tissue, involving connective tissue, fat and vessels alike, as well as the mucosa of the duodenum and the capsule of the left adrenal gland. Many veins contained thrombi. Finely granular, blue-staining material, which was considered to be calcium soap, was present in many of the necrotic areas. When such an area was stained with scarlet red a large amount of fat was revealed

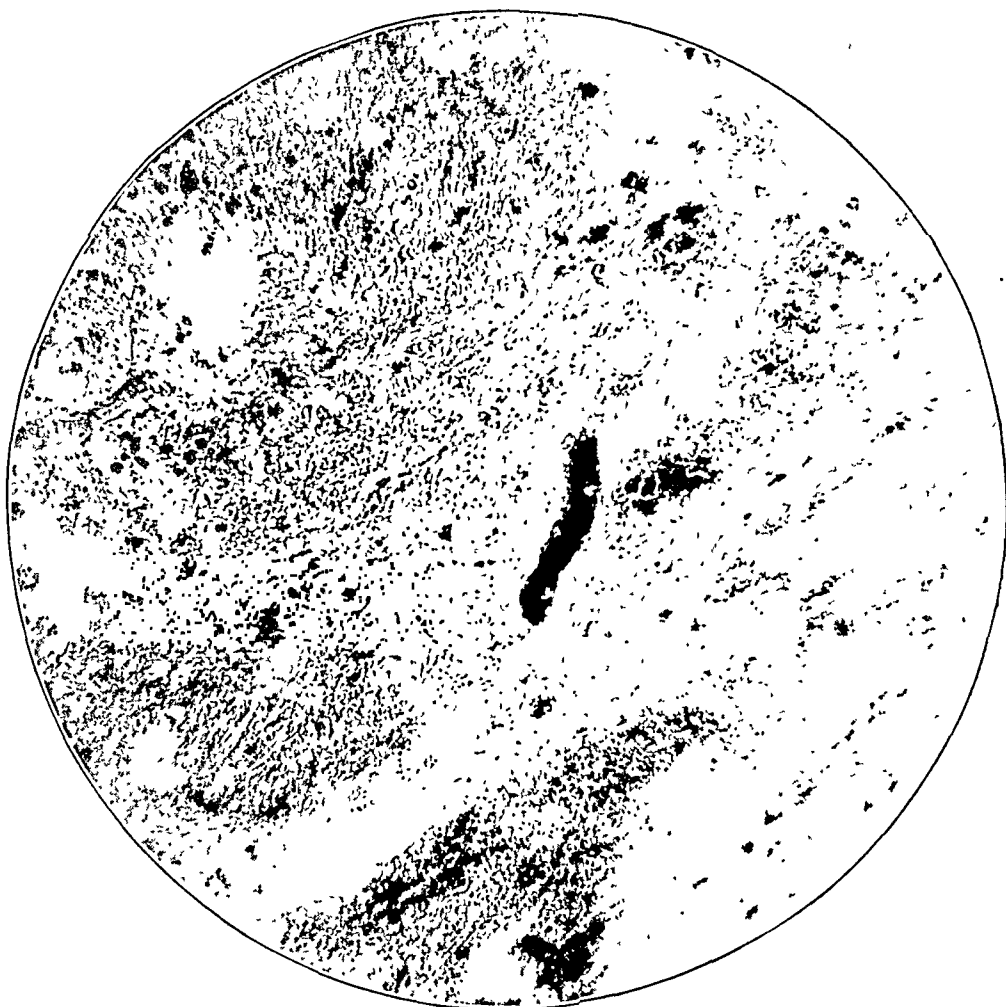


Fig. 1.—A section of the pancreas through an area of necrosis, in which the veins and lymphatic vessels are filled with fat. Scarlet red;  $\times 100$ .

in the necrotic lesions, much of which was within small veins, venules and lymphatics. Some of these appeared to be completely filled (fig. 1).

The lungs contained areas of atelectasis, and the alveolar capillaries were dilated. The most striking changes were seen in sections stained with scarlet red. Many vessels contained fat droplets of various sizes. Some were fine (about the size of blood platelets), and others were so large that they completely filled the capillaries (fig. 2). Layers of fat droplets adhering to the intima were noted occasionally in the larger vessels (fig. 3). In some areas the vessels contained few fat droplets or none at all.

In sections of the heart stained with scarlet red most of the small veins were found to be completely filled with intensely staining lipids. Some of the capillaries were similarly filled, but the arteries were free of droplets. About one half of the muscle fibers contained fine fat droplets in the cytoplasm in a segmental arrangement typical of fatty degeneration. In sections of renal tissue stained with hematoxylin and eosin little change was observed in the glomeruli and the vessels. The epithelium of the convoluted tubules was finely granular and exhibited changes characteristic of early degeneration. In sections stained with scarlet red many fat droplets were seen in the glomerular capillaries; some

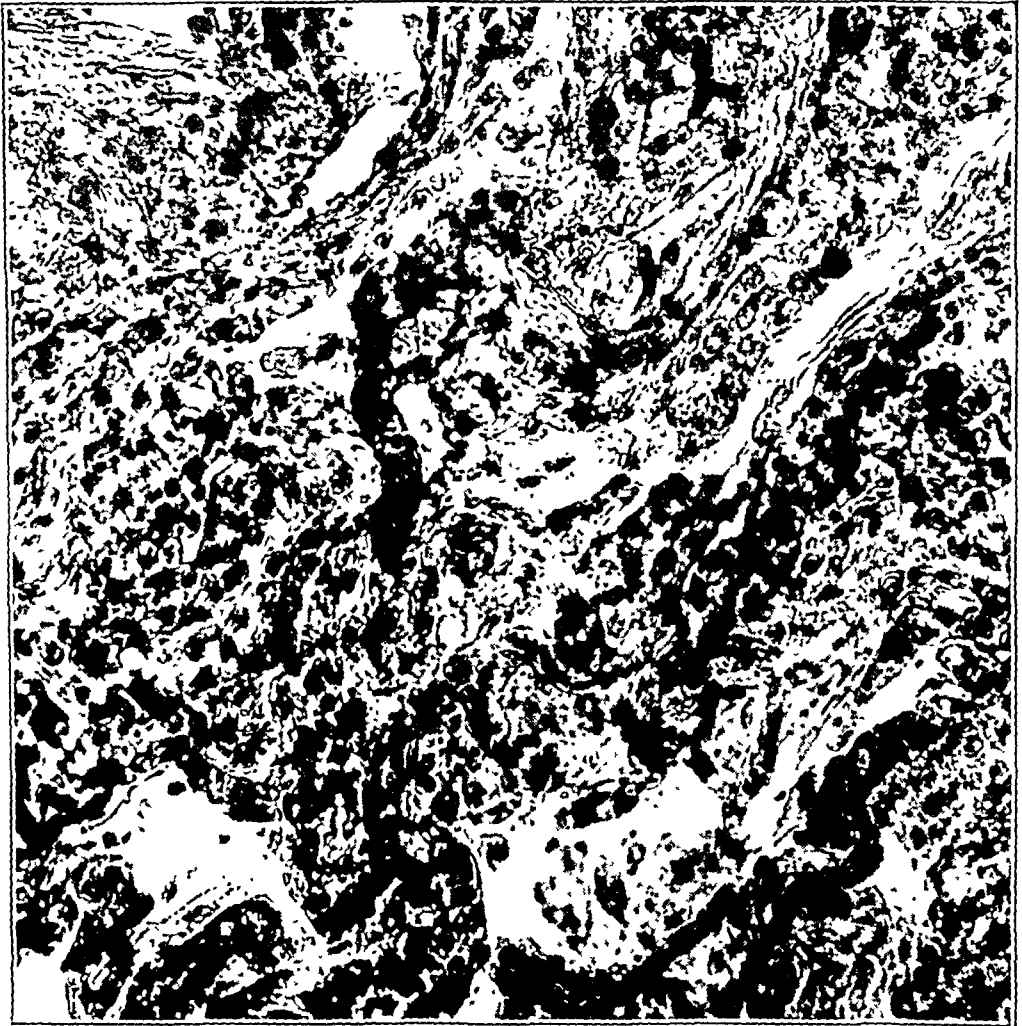


Fig. 2.—Pulmonary capillaries containing fat.  $\times 500$ .

appeared completely filled. Droplets also occurred in many of the veins. Fine droplets of lipid material were present in the tubular epithelium.

The cytoplasm of the liver cells contained many large and small vacuoles. No noteworthy changes were visible in the blood vessels. A definite increase of connective tissue and a few mononuclear cells were noted in the periportal spaces. Liver cells stained with scarlet red displayed diffuse fatty changes in the cytoplasm, but little fat was seen in the vascular channels.

The anatomic diagnosis included chronic cholecystitis, cholelithiasis, acute pancreatic necrosis, hyperlipemia, fat embolism and pulmonary atelectasis.

Fat embolism and hyperlipemia were observed in this case. No antemortem determinations of serum calcium were made. Definite fat embolism of the pulmonary and renal vessels was demonstrated. Fat embolism of the cerebral vessels was probably present, but it is questionable whether it caused the tetany. The carbon dioxide-combining power of 47 volumes per cent eliminated alkalosis as the causative factor. The cause of the tetany remains uncertain.

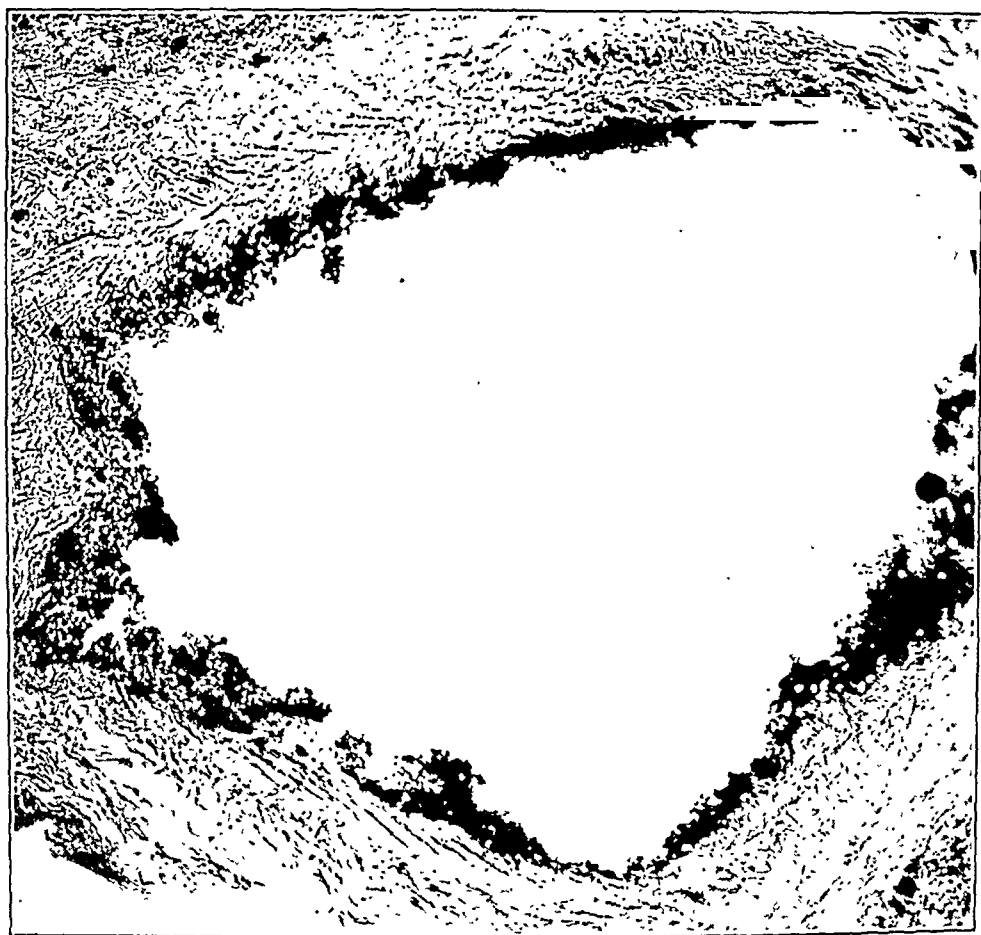


Fig. 3.—Fat droplets adherent to the intima of a pulmonary vessel.  $\times 135$ .

#### CALCIUM AND FAT NECROSIS

The possibility of hypocalcemia due to deposition of calcium in the necrotic lesions was also considered as a possible cause of the tetany in the case just reported. The total calcium content of a portion of the pancreas and peripancreatic fat was determined. Unfortunately, only a 2 Gm. specimen was analyzed. This contained 10.5 mg. of calcium, or 525 mg. per hundred grams of tissue. As there was easily 400 Gm. of necrotic tissue, some 2,000 mg. of calcium might be assumed to have been present in combination with fatty acids as soaps. Since only a

2 Gm. sample was analyzed, too much reliance cannot be placed on these figures. However, there can be little doubt that the calcium in the necrotic tissue was enormously increased over the amount in normal tissue.

In a second instance (case 5 of table 2), in which acute pancreatitis followed surgical removal of a calculus from the common duct, the duration of symptoms was less than twenty-four hours and the grossly evident necrosis was confined to the pancreas and the fatty tissue immediately surrounding it. A mass of tissue weighing 210 Gm., taken from these structures yielded 200 mg. of calcium. More recently a third instance (case 6 of table 2) has been studied. The clinical history was not cleancut as to the duration of the disease, but the patient had been ill for seven days. Necropsy revealed obesity and widespread fat necrosis, involving the omentum, the mesentery and the retroperitoneal

TABLE 1.—*The Calcium Content of Lesions in Acute Pancreatic Necrosis, as Compared with That of Pancreatic Tissue*

Case	Peripancreatic		Total Amount of Calcium (Mg.) in Pancreas Plus 2 Kg. of Adjacent Fatty Tissue	
	Calcium Content of Pancreas, Mg. per 100 Gm. of Wet Tissue	Fatty Tissue, Mg. per 100 Gm. of Wet Tissue		
1 (control) .....	5.6	2.6	Estimated maximum	58
2 (control) .....	5.3	2.3	Estimated maximum	52
3 (control) .....	6.0	3.6	Estimated maximum	78
4 .....	525.0	.....	Estimated	1,500
5 .....	.....	.....		200*
6 .....	178.0	152.0		1,732

\* In this case the disease was of less than twenty-four hours' duration.

fat. The pancreas and involved fat, with a total weight of 2,250 Gm., was ground three times, and three samples of 5 Gm. each were taken. These samples contained almost identical amounts of calcium, with an average of 3.75 mg., or 75 mg. per hundred grams of tissue. The total amount of calcium was estimated at 1,732 mg. Separate samples of pancreas, peripancreatic fat and omentum were analyzed. These contained 178, 152 and 36 mg. of calcium per hundred grams of tissue, respectively (table 1).

Samples of pancreatic tissue from 2 moderately obese men (cases 1 and 2 of table 2) aged 43 and 68, respectively, and 1 woman (case 3 of table 2) aged 62 were used as controls. They contained 5.6, 5.3 and 6 mg. of calcium per hundred grams of tissue, respectively. Specimens of peripancreatic fat yielded 2.6, 2.3 and 3.6 mg., respectively. As the normal pancreas rarely weighs over 100 Gm., it is evident that in cases of fat necrosis, an excessive amount of calcium collects in the pancreatic tissue.

## TETANY

It is assumed that the average human being has a total blood volume of 6,000 cc. and that the total serum calcium is about 600 mg., of which 250 to 300 mg. is diffusible. If only 100 mg. of diffusible calcium is lost more or less rapidly, the concentration of serum calcium may drop to 8.3 mg. per hundred cubic centimeters if the calcium is not replenished from reserves. The extracellular body fluids amount to approximately three times the plasma volume and constitute a reservoir of calcium which is in equilibrium with that in the blood.<sup>11</sup>

Estimates of the total amount of calcium in the extracellular fluids have been made by studies of transudates<sup>12</sup> which revealed an average content of 7.5 mg. per hundred cubic centimeters, or a total of 750 mg. of calcium. This would tend to offset the drop in serum calcium. It may be noted in table 1 that in 1 case (C. L.) the 1,732 mg. of calcium deposited in the necrotic pancreas and surrounding fat was greater than the total normal amount of calcium in the blood and tissue fluids.

Another problem of importance is to determine how quickly the parathyroid glands, acting through solution of parathyroid, may replenish lost serum calcium. In experimental animals twenty to eighteen hours elapses after an injection of parathyroid extract before serum calcium reaches its maximum level.<sup>13</sup> No experimental evidence was found that gave any clue as to how quickly the calcium level would return to normal in an intact animal after a sudden decrease of serum calcium.

Three instances of tetany associated with acute pancreatic necrosis have been reported. Bertelsman<sup>14</sup> operated on a 33 year old white woman who had suppurative cholecystitis and acute pancreatic necrosis. On the second day after operation she had tetanic convulsions. Serum calcium was not determined. Intravenous administration of calcium and solution of parathyroid was followed by the prompt disappearance of tetany. The patient recovered, and a year later no clinical evidence of disturbance in calcium metabolism was apparent. Bertelsman expressed the belief that the tetany was due to the pancreatitis but did not discuss the mechanism.

Cibert and Plauchu<sup>15</sup> noted severe tetany in a man aged 32 in whom acute hemorrhagic pancreatitis was revealed during an exploratory lapa-

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14. Bertelsman, R.: Postoperative Tetanie bei eitriger Cholecystitis und akuter Pankreasnekrose, *Zentralbl. f. Chir.* **54**:324, 1927.

15. Cibert, J., and Plauchu, M.: Pancréatite aiguë hémorragique et tétanie, *Lyon méd.* **152**:587, 1933.

rotomy thirty-nine hours after the onset of illness. The tetany ceased twenty-four hours after operation. They discussed only the possibility of the tetany being due to vomiting, with the resultant loss of chlorides and the accompanying loss of calcium.

Amano and Murata<sup>16</sup> observed tetany in a 29 year old Japanese woman seen on the second day of her illness. The level of serum calcium was 10.3 mg. per hundred cubic centimeters, but nevertheless intravenous administration of calcium was followed by cessation of the tetany. The patient was subjected to an operation. Extensive fat necrosis was found, a cholecystotomy was done and recovery ensued. The authors suggested three possible causes of the tetany: (1) disturbance of the external secretion of the pancreas; (2) disturbance of the internal secretion of the pancreas, and (3) intoxication due to peritonitis.

#### REPORT OF TWELVE CASES OF ACUTE PANCREATIC NECROSIS

We have studied to date a series of 12 cases in which we are convinced both by clinical findings and by the values for urinary diastase (method of Fabricius and Moeller, cited by Foged<sup>17</sup>) and/or those for blood amylase (method of Somoygi, cited by Elman<sup>18</sup>) that there was evidence of acute pancreatic necrosis. Total serum lipids (not including cholesterol) were determined in 6 of the 12 cases. Brief clinical summaries follow. (The results of the calcium and lipid studies are given in table 2.)

CASE 1.—B. W., a 30 year old white woman, was admitted to the hospital on March 4, 1940 because of severe persistent midepigastic pain of nine hours' duration. Similar attacks lasting about one-half hour had occurred for the past ten days. On admission the patient appeared acutely ill; respirations were shallow, and both upper quadrants of the abdomen were rigid and tender. The temperature was 101 F., the pulse rate 118 per minute and the blood pressure 95 mm. of mercury systolic and 60 mm. diastolic. The leukocyte count was 18,300 (94 per cent neutrophils). The urine contained an occasional pus cell. The value for urinary diastase twenty-six hours after the onset of illness was 1,200 units.<sup>19</sup> The Wassermann reaction of the blood was negative. The patient received morphine for the relief of pain and fluids intravenously as needed. Recovery appeared to be complete, and she was discharged on March 12.

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16. Amano, M., and Murata, M.: Tetanie bei akuten Abdominalerkrankungen, *Zentralbl. f. Chir.* **63**:694, 1936.

17. Foged, J.: The Diagnostic Value of Urine Diastase, *Am. J. Surg.* **27**: 439, 1935.

18. Elman, R.: The Variations of Blood Amylase During Acute Transient Disease of the Pancreas, *Ann. Surg.* **105**:379, 1937.

19. The unit of diastase is the same as that used by Foged, which he based on Wolgemuth's definition, "that solution, 1 cm. of which, under given conditions . . . is able to break down 1 cm. of 1-promille dissolved starch."<sup>17</sup>



CASE 2.—O. B., a 36 year old obese white woman, entered the hospital on March 17, 1940 with the complaint that four days previously she had had a sudden severe pain in the abdomen at the level of the umbilicus. The pain had persisted but had gradually become dull in character. She had vomited from six to eight times a day. On admission her temperature was 99.8 F. and her pulse rate 80 per minute. Her blood pressure was 110 systolic and 75 diastolic. Examination revealed generalized tenderness and guarding of the abdomen, with the point of maximum tenderness in the midepigastrium. The leukocyte count was 11,900. A few pus cells were found in the urine. The urinary diastase reading on entry was 1,200 units, and two days later the value for blood amylase was 548 mg.<sup>20</sup> The patient continued to have abdominal pain and tenderness, accompanied by daily elevations of temperature to between 99.4 and 99.8 F. A cholecystogram disclosed many small rarefactions. On April 4 the gallbladder, containing many small calculi, was removed. No evidence of former pancreatitis was seen at operation. Recovery was uneventful, and the patient was discharged on April 17.

TABLE 2.—*The Values for Serum Calcium and Serum Lipids in Clinical Acute Pancreatic Necrosis\**

Case	Serum Calcium, Mg. per 100 Cc.															Lipids, Mg. per 100 Cc.	
	1	2	3	Time Elapsed Since Onset of Illness (Days)	4	5	6	7	8	9	10	11	12	13	14		15
1.....			7.0	.....	.....	.....	8.0	.....	.....	9.4	.....	.....	9.4	.....	.....	.....	584
2.....				.....	.....	.....		.....	.....		.....	.....		.....	.....	.....	167
3.....	9.6	.....		.....	.....	.....		.....	.....		.....	.....		.....	.....	.....	197
4.....			8.3	.....	.....	.....		.....	9.7	.....	.....	.....		.....	.....	.....	284
5.....			9.7	9.7	.....	.....		.....		.....	.....	.....		.....	.....	.....	.....
				9.4	.....	.....		.....		.....	.....	.....		.....	.....	.....	.....
6.....			8.7	.....	.....	.....	8.4	.....	.....	.....	.....	.....		.....	.....	.....	544
7.....	9.5	.....	9.1	.....	9.4	.....		.....		.....	.....	.....		.....	.....	.....	.....
			8.5	8.5	.....	.....		.....		.....	.....	.....		.....	.....	.....	.....
8.....	10.3	.....		.....	.....	.....		.....		.....	.....	.....		.....	.....	.....	.....
9.....				.....	.....	.....		7.9	7.7	.....	7.4	7.6	.....		13.4	11.2	381
				.....	.....	.....			7.7	.....		8.1	.....	10.1			.....
10.....		9.0	.....	8.9	8.8	.....		.....		.....	.....	.....		.....	.....	.....	.....
11.....				9.7	.....	.....		.....		.....	.....	.....		.....	.....	.....	.....
12.....					9.3	.....		.....		.....	.....	.....		.....	.....	.....	.....

\* The serum lipids were determined at the time of the first measurement of serum calcium in 6 of 12 cases.

CASE 3.—T. R., a 31 year old obese white woman, entered the hospital on March 23, 1940 because of severe, sharp, continuous pain in the epigastrium during the preceding twelve hours. The pain radiated through to the back. She had vomited about ten times. On examination the patient appeared to be in shock; the skin was cold and clammy; the temperature was 97 F., the pulse rate 72 per minute and the blood pressure 108 systolic and 80 diastolic. There was extreme tenderness but no rigidity in the epigastrium. The leukocyte count was 11,100. The urine contained albumin (3 plus). On entry the value for urinary diastase was 1,200 units and that for blood amylase 2,030 mg. The Wassermann reaction of the blood was negative. The treatment was conservative; 10 cc. of a 10 per cent solution of calcium gluconate was given intravenously every four hours for

20. The expression of the value for blood amylase in milligrams is based on Somogyi's sugar reduction method, cited by Elman.<sup>18</sup> The activity of the amylase is measured by the hydrolysis of a starch solution under given conditions, and the result is expressed in milligrams of sugar per hundred cubic centimeters of blood.

three days. Because of this therapy only one determination of serum calcium was made. The temperature varied from 101 to 102 F. for the first four days, then gradually returned to normal. The patient recovered and was discharged on April 4.

CASE 4.—V. C., a 45 year old Mexican, came to the hospital on March 30, 1940, after three days of severe epigastric pain and vomiting. He had been drinking heavily for a month. The temperature was 102.8 F., the pulse rate 130 per minute and the blood pressure 124 systolic and 80 diastolic. Both upper quadrants of the abdomen were rigid, and the left upper quadrant was extremely tender. The leukocyte count was 10,450. The icteric index was 38. The urinary diastase reading was 1,200 units. The patient received morphine and intravenous injections of a solution of dextrose. Improvement was rapid, and he was discharged on April 11.

CASE 5.—M. E., a 57 year old white woman, was admitted to the hospital on April 21, 1940. She gave a history of severe epigastric pain of four days' duration, with associated nausea and vomiting. The skin and scleras were slightly icteric (icteric index, 50). The abdomen was soft, but there was tenderness in the right upper quadrant, particularly over the gallbladder. The temperature was 98 F., the pulse rate 60 per minute and the blood pressure 165 systolic and 85 diastolic. The leukocyte count was 16,000. The value for urinary diastase was 600 units and that for blood amylase 2,835 mg. The patient received sedatives and intravenous injections of fluids; before the results of the serum calcium determinations were known, calcium gluconate was given intravenously. She improved and was discharged on May 18.

CASE 6.—J. E., a 50 year old white man, was admitted on April 27, 1940. He complained that he had awakened eight hours before admission with severe epigastric pain which radiated to the right upper quadrant of the abdomen and which was followed by vomiting and feverish sensations. He gave a history of chronic alcoholism and particularly heavy drinking for several days preceding the onset of illness. He was noticeably icteric (icteric index, 23). The gallbladder was enlarged and tender. The middle portion of the epigastrium was moderately tender but not rigid. The temperature was 103 F. and the pulse rate 120 per minute. The urine contained a trace of albumin and a few pus cells. The leukocyte count was 14,600. The value for urinary diastase was 600 units and that for blood amylase 1,425 mg. The Wassermann reaction of the blood was negative. Calcium gluconate was administered intravenously in addition to the usual conservative treatment. Icterus persisted, but otherwise the patient improved rapidly and was discharged on May 7.

CASE 7.—L. K., a 26 year old man, was admitted to the hospital on April 9 1940. Eight months before admission he had been in the hospital for distress of indefinite origin in the upper part of the abdomen. This had recurred several days before his second entry, and he had become jaundiced. The right upper quadrant of the abdomen and the epigastrium were tender and rigid. The icteric index was 80. He improved somewhat, but on May 6 he had a sudden onset of epigastric pain. Six hours after the onset the blood amylase reading was 218 mg. The value for urinary diastase was normal, and that for serum calcium was 9.5 mg. per hundred cubic centimeters. On the second day of illness the value for urinary diastase was 1,200 units. Calcium gluconate was administered intravenously, but the level of serum calcium fell slightly on the second and third day, as shown in table 2. The patient improved enough that on May 18 his diseased

gallbladder, containing multiple calculi, was removed. The pancreas was firm, enlarged and contained many pinhead-sized areas of healing fat necrosis. No stone was found in the common duct. Recovery was uneventful, and the patient was discharged on June 13.

CASE 8.—W. D., a 52 year old Negro, was admitted to the hospital on May 21, 1940 because of epigastric and paraumbilical pain, which began suddenly seven hours before entry. The pain had increased in severity and had spread throughout the abdomen, which was boardlike in its rigidity. The point of maximum tenderness was in the midepigastrium. The temperature was 99 F., the pulse rate 84 per minute and the blood pressure 140 systolic and 96 diastolic. The leukocyte count was 15,600. The urine contained albumin (1 plus). On microscopic examination an occasional cast and a few pus cells were seen. The value for urinary diastase was 1,200 units and that for blood amylase 1,961 mg. The patient received morphine and a solution of dextrose intravenously. He felt much better the next morning and left the hospital without consent ten hours after entry.

CASE 9.—J. B., a 63 year old Mexican, entered the hospital on May 23, 1940. He gave a history of severe epigastric pain, associated with nausea of three days' duration. The temperature was 101.6 F., the pulse rate 128 per minute and the blood pressure 128 systolic and 80 diastolic. Abdominal tenderness was extreme and generalized. The urine contained albumin (3 plus) and a few pus cells. The leukocyte count was 7,200. On the seventh day of illness the value for urinary diastase was 600 and that for blood amylase 125 mg. He received sedatives and fluids intravenously, including calcium gluconate beginning on the ninth day of hospitalization. Improvement was steady. The patient left the hospital free from any symptoms; he failed to return to the clinic for further checking, although he was urged to do so.

CASE 10.—J. M., a 23 year old Mexican, was brought to the hospital on May 26, 1940, after an accident in which the automobile in which he was riding had collided with a train. The patient appeared to be in shock. His breath had an alcoholic odor. The rectal temperature was 98.2 F., the pulse rate 96 per minute and the blood pressure 60 systolic and 40 diastolic. There were many fresh abrasions of the skin. The leukocyte count was 19,800, with 96 per cent neutrophils. The value for urinary diastase on the second day of illness was 400 units. He received sedatives and fluids intravenously. Improvement was steady, and he was discharged on June 10.

CASE 11.—A. D., a 39 year old white man, was admitted to the hospital on June 10, 1940 because of persistent nonradiating epigastric pain of five days' duration. He had been drinking heavily for some time before the onset of pain. On admission his temperature was 99 F., his pulse rate 100 per minute and his blood pressure 136 systolic and 96 diastolic. Both upper quadrants of the abdomen were tender but not rigid. The leukocyte count was 10,500. The value for urinary diastase was 400 units and that for blood amylase 434 mg. He received a solution of dextrose intravenously and sedatives. The patient apparently recovered and was discharged on June 20.

CASE 12.—D. C., a 35 year old white woman, entered the hospital on Aug. 22, 1940, complaining of severe epigastric pain of thirty-six hours' duration, accompanied by repeated vomiting. The abdomen was distended, and there was extreme tenderness over the upper half. The temperature was 98 F., the pulse rate 100

per minute and the blood pressure 107 systolic and 80 diastolic. The leukocyte count was 9,600. The urine contained a faint trace of albumin. The value for urinary diastase was 2,400 units and that for blood amylase 1,618 mg. The calcium content of the blood was not determined until the fifth day of illness. The patient received the usual conservative treatment, improved rapidly and was discharged on September 2.

#### COMMENT

In only 1 of the 12 cases just summarized was the value for serum calcium above 10 mg. per hundred cubic centimeters, and in 7 cases it was below normal. The range was 7.0 to 8.8 mg. per hundred cubic centimeters. This was not unexpected in view of the amounts of calcium found in the lesions at necropsy in the first 3 cases reported in this paper. Values for serum calcium determined during the first day of illness (3 cases) were normal. In 1 case (L.K.) the value subsequently fell to 8.5 mg. per hundred cubic centimeters. In another (T.R.) the patient was in shock and intravenous calcium therapy was instituted, so that no further determination of calcium was made. In 6 of the 7 cases in which the value for serum calcium was low the sub-normal level was reached on the third to the sixth day of illness. It is difficult to understand why the level of calcium remained low in 1 case (J. B.) for two days after calcium was given intravenously.

If it were possible to determine the serum calcium daily from the onset of the disease a greater number of low values might be obtained, but normal values would be expected unless the amount of fat necrosis was fairly extensive. It is known from the work of Rich and Duff<sup>21</sup> that both trypsinogen and lipase are concerned in the production of pancreatic necrosis. Our observations at necropsy taught us that either hemorrhagic lesions or fat necrosis may predominate. If the lesions are principally hemorrhagic there may not be enough fatty acids formed to require any appreciable amount of calcium in the formation of soaps.

Serum lipids were within normal range. We failed to observe any such increases in serum lipids as those reported by Binet and associates<sup>8</sup> and by Brunner.<sup>9</sup> It would appear that instances of severe hyperlipemia are rare. We also studied all cases of acute pancreatic necrosis for which there were necropsy records within recent years at the Los Angeles County Hospital. Specimens of lung tissue fixed in solution of formaldehyde U. S. P. were available in only 6 cases. Stains specific for fat revealed a few scattered droplets in the pulmonary vessels in 1 case. It seems inevitable that some absorption of fat and fatty acids must occur in extensive areas of necrosis. At least it is evident in 1 of our cases that abundant fat droplets were present in veins and lymphatics

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21. Rich, A. R., and Duff, G. T.: Experimental and Pathological Studies on the Pathogenesis of Acute Hemorrhagic Pancreatitis, *Bull. Johns Hopkins Hosp.* 58:212, 1936.

in the necrotic areas. It is questionable whether fatty acids by their own weak acidity contribute to the toxicity of the patient even if absorbed. The absorption of neutral fat, however, might be an important cause of death, in view of the autopsy observations in the case in which fat embolism occurred. Whether lack of available calcium and failure, therefore, to form soaps might favor absorption of the oleic fraction of the fatty acids at the point of origin of the acids is a matter for consideration.

#### CALCIUM THERAPY

The importance of calcium as a therapeutic agent cannot be evaluated, as it was used in only 3 of the last 12 cases reported, and, furthermore, it was employed only in conjunction with other therapeutic agents. In these 12 cases, in which there was a clinical picture of acute pancreatic necrosis, the record of therapeutic accomplishment is more favorable than one usually obtains. It must, of course, be recognized that the favorable outcome may be purely coincidental. We believe, however, that the use of calcium is indicated in cases of acute pancreatic necrosis, because it seems logical to assume that a plentiful supply of available calcium is desirable in order to facilitate the formation of calcium soaps in situ without undue depletion of the serum calcium.

#### SUMMARY

1. A case of acute pancreatic necrosis, tetany and fat embolism is reported.
2. A total in excess of 1,700 mg. of combined calcium was found in the pancreas, plus 2 Kg. of peripancreatic fat in another case of acute pancreatic necrosis (normal value, 78 mg. or less).
3. The level of serum calcium was below normal in 7 of 12 cases in which a diagnosis of acute pancreatic necrosis was made.
4. The value for serum lipids was normal in 6 of the aforementioned 12 cases.
5. Calcium therapy was employed in 3 of the 12 cases.

#### CONCLUSIONS

1. Fat embolism or severe hyperlipemia is rare in cases of acute pancreatic necrosis.
2. Considerable quantities of calcium may be present in the lesions in cases of acute pancreatic necrosis.
3. A moderate fall in the level of serum calcium of patients with acute pancreatic necrosis may occur between the third and the eleventh day of illness.
4. The effectiveness of calcium therapy should be evaluated after use in a larger number of patients.

# CAPSULAR POLYSACCHARIDE IN THE BLOOD OF PATIENTS WITH PNEUMOCOCCIC PNEUMONIA

DETECTION, INCIDENCE, PROGNOSTIC SIGNIFICANCE AND  
RELATION TO THERAPIES

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We recently reported on the systematic examination for circulating capsular polysaccharide in the blood of 26 patients treated for pneumococcic pneumonia.<sup>1</sup> It is generally recognized that the presence of bacteremia increases the gravity of the prognosis of the disease. It appeared from our earlier observations that the occurrence of free polysaccharide, which is more rapidly detectable than bacteremia, makes the prognosis even graver.

In this paper are reported the cases of 109 additional patients with pneumonia due to *Pneumococcus* type I, II, III, IV, V, VII or VIII and are presented the data on 135 patients frequently studied for the presence of polysaccharide.

## MATERIALS AND METHODS

The patients, who had ample clinical, and usually roentgenologic, evidence of lobar pneumonia, were studied in the pneumonia service of Harlem Hospital. Before treatment was instituted samples of sputum for typing and of blood for

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1. Bukantz, S. C.; Bullova, J. G. M., and de Gara, P. F.: Detection of Capsular Polysaccharide in the Blood of Pneumococcic Pneumonias: Prognosis and Therapy, *Proc. Soc. Exper. Biol. & Med.* **41**:250, 1939; The Balance Between Capsular Polysaccharide and Antibody in Relation to Prognosis and Therapy of Pneumococcic Pneumonia, *Ann. Int. Med.* **14**:1348, 1941.

bacteriologic and immunologic examination were taken. After the types of pneumococci were known the patients were rotated for therapy with serum, with sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) or with the two in combination. Whenever possible samples of blood were taken on the mornings of the second, third, fifth, eighth, eleventh and fourteenth days of hospitalization. When the disease persisted beyond the fourteenth day, samples of blood were examined at intervals determined by the course of the disease. The level of sulfapyridine in the blood was determined every forty-eight hours by the method of Bratton and Marshall<sup>2</sup> employing a photoelectric colorimeter. In some cases, urine, chest fluid or spinal fluid was studied.

*Detection of Circulating Capsular Polysaccharide.*—In the first 26 cases the method of Dochez and Avery<sup>3</sup> was used to determine the presence of circulating capsular polysaccharide.<sup>1</sup> In the subsequent 109 cases, because the "optimal" concentrations of antibody for detection of circulating capsular polysaccharide for each

AGGLUTININ CONTROLS			AGGLUTININ TEST						PRECIPITIN TEST		
POS	NEG	0.5 CC. HOMOLOGOUS ORGANISMS (OPTIMAL DILUTION IN SALINE)						0.5 CC. HOMOLOGOUS SSS			
(11)	(12)	(13)	(14)	(15)	(16)	(17)	(18)	(19)	(20)		
HOM RS.	SALINE	1:4*	1:8	1:16	1:32	1:64	1:4*	1:8	1:16		
		PATIENT'S SERUM						PATIENT'S SERUM			
HOM RS.	HET RS.	SALINE	HOM RS.	HET RS.	HOM RS.	HET RS.	HOM SSS.	HET SSS.	HET SSS.		
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)		
PATIENT'S SERUM (UNDILUTED)			HOM SSS	HET SSS	SALINE		SALINE		PATIENT'S SERUM		
POLYSACCHARIDE TEST			POSITIVE & NEGATIVE SERUM & POLYSACCHARIDE CONTROLS						PRECIPITIN CONTROL		

0.5 CC. OF EACH REAGENT IN 10 X 75 MM. TUBES. CENTRIFUGATION - 2000 RPM - 30 MINUTES

RS - RABBIT SERUM (OPTIMAL DILUTION IN PHYSIOLOGIC SOLUTION OF SODIUM CHLORIDE)

SSS - CAPSULAR POLYSACCHARIDE (OPTIMAL DILUTION IN PHYSIOLOGIC SOLUTION OF SODIUM CHLORIDE)

HOM - HOMOLOGOUS

HET - HETEROLOGOUS

\* FINAL DILUTION

Fig. 1.—Technic of detection of pneumococcic antigen-antibody balance in blood.

of the types of pneumococci under investigation had been determined,<sup>4</sup> it was unnecessary to make any dilutions of patient's serum. Five-tenths cubic centimeter of patient's serum is delivered into each of three 10 by 75 mm. pyrex tubes. Five-tenths cubic centimeter of the optimal dilution of homologous type-specific rabbit antibody solution is added to one tube, 0.5 cc. of a heterologous rabbit antibody solution to a second tube and 0.5 cc. of physiologic solution of sodium chloride to the third tube. Six additional positive and negative control tubes are prepared as indicated in figure 1. All tubes are centrifuged at 2,000

2. Bratton, A. C., and Marshall, E. K., Jr.: A New Coupling Component for Sulfanilamide Determination in Blood and Urine, *J. Biol. Chem.* **128**:537, 1939.

3. Dochez, A. R., and Avery, O. T.: Elaboration of Specific Soluble Substance by *Pneumococcus* During Growth, *J. Exper. Med.* **26**:477, 1917.

4. Bukantz, S. C., and de Gara, P. F.: The Detectability of Pneumococcal Polysaccharide and Antibody in Blood, Broth and Saline Solution (Optimal Concentration of Antigen and Antibody), *J. Immunol.* **39**:195, 1940.

revolutions per minute for thirty minutes.<sup>5</sup> When capsular polysaccharide is present in the serum, a precipitate appears in the first tube but not in the second and third. In all determinations the controls yielded the expected results. A precipitate may appear in the first tube because of antirabbit antibody present in the patient's serum during the course of serum sickness. In such instances, however, the second tube serves as a control, since it contains rabbit protein in contact with the patient's serum and therefore also yields a precipitate.

# RESULTS

*Incidence of Circulating Capsular Polysaccharide.*—In Relation to Type of Pneumococcus and Severity of Disease: In table 1 are listed by type of pneumococcus the patients with detectable circulating cap-

TABLE 1.—*Mortality Rate for All Patients and for Patients with a Positive Reaction for Circulating Capsular Polysaccharide*

Type of Pneumococcus	Total Series		Percentage of Deaths	Patients with Positive Reactions for Circulating Capsular Polysaccharide		Percentage of Deaths
	Patients	Deaths		Patients	Deaths	
I.....	32 5*	1 0*	3.1	0	0	
II.....	4 2*	0 0*	....	0	0	
III.....	40 7*	8 3*	20.0 43.0*	11 6*	7 3*	
IV.....	1 1*	1 1*	....	0	0	
V.....	9 3*	2 1*	....	0	0	
VII.....	33 10*	3 3*	9.1 30.0*	3 2*	2 2*	
VIII.....	16 3*	1 1*	....	2 2*	1 1*	
Total.....	135 31*	16 9*	11.8 29.1*	16 10*	10 6*	62.6 60.0*

\* Bacteremia present.

sular polysaccharide. The incidence of bacteremia and mortality is noted. All patients were accepted in the order of admission, without omissions because of mildness of disease. Circulating capsular polysaccharide was detected in the blood of 16 of the 135 patients (11.8 per cent). Only in the groups of patients with pneumonia due to Pneumococcus type I, III, VII or VIII were more than 15 patients studied. Circulating capsular polysaccharide was most frequently found among patients suffering from type III pneumococcus pneumonia, 11 of 40, or 27.5 per cent. Such patients were 68.7 per cent of all whose serum gave a

5. de Gara, P. F.; Bukantz, S. C., and Bullowa, J. G. M.: Pneumococcal Capsular Polysaccharide in Urine: Detection by Precipitation and Centrifugation, J. Immunol. **37**:305, 1939.



positive reaction for capsular polysaccharide (11 of 16). This substance was also found in the serum of patients suffering from pneumonia due to *Pneumococcus* type VII or VIII—in 3, or 9.1 per cent, of 33 with type VII *pneumococcus* pneumonia and in 2, or 12.5 per cent, of 16 with type VIII *pneumococcus* pneumonia. The patients suffering from pneumonia due to *Pneumococcus* type I or VII were rated for the severity of disease on admission on the scale of Bullowa.<sup>6</sup> There were 32 patients with type I *pneumococcus* pneumonia, of whom 3 were rated as severely (50), 15 as moderately (50 to 70) and 14 as mildly (70 plus) ill on admission. Of 33 patients suffering from type VII *pneumococcus* pneumonia, 4 were severely, 10 moderately and 19 mildly ill. The patients with type I *pneumococcus* pneumonia were at least as severely stricken when first observed as were those with pneumonia due to the type VII *pneumococcus*.

**In Relation to Bacteremia:** In 31 of the 135 cases, or 23 per cent, bacteremia was present on admission. The incidence of bacteremia among the cases in which there was a positive reaction for capsular polysaccharide in the blood was 10 of 16, or 62.5 per cent, and among cases in which a negative reaction was obtained the incidence was 21 of 119, or 17.6 per cent. In 10, or 32.2 per cent, of 31 cases in which bacteremia was present the reaction for circulating capsular polysaccharide was positive, while it was positive in only 6, or 5.9 per cent, of 104 cases in which there was no associated bacteremia. It appears that while such a reaction was positive in approximately only one third of the cases in which bacteremia occurred, in almost two thirds of the cases in which the reaction was positive bacteremia was also present.

**In Relation to Age:** Of the 89 patients suffering from pneumonia due to *Pneumococcus* type III, VII or VIII, circulating capsular polysaccharide was found more frequently in those over 40 years of age (table 2 *A*). Only 1 of the 16 patients showing this substance in the blood was younger. Ten of the 16 were past 50 years of age (table 4).

**In Relation to Sex and Duration of Disease:** The first 16 cases of pneumonia caused by *Pneumococcus* type III, VII or VIII were confined almost entirely to the ward for male patients so that for determination of sex distribution only the last 73 cases have been analyzed. The distribution of cases in which there was a positive reaction for capsular polysaccharide in the blood was approximately the same for both sexes (table 2 *B*).

Although 56.3 per cent of the patients were first observed on the first to the fourth day of disease, only 6 (37.5 per cent) of the 16

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6. Bullowa, J. G. M.: Use of Antipneumococcic Refined Serum in Lobar Pneumonia, J. A. M. A. 90:1349 (April 28) 1928.

TABLE 2.—*Incidence of Detectable Circulating Capsular Polysaccharide in Relation to Age, Sex and Day of Disease on Which Patient Was Admitted to Hospital*

A. RELATION TO AGE IN EIGHTY-NINE PATIENTS WITH PNEUMONIA DUE TO PNEUMOCOCCUS TYPE III, VII OR VIII

Age of Patient	Total Series		Circulating Capsular Polysaccharide Present	
	Number of Patients	Percentage	Number of Patients	Percentage
Under 40 years.....	34	38.1	1	2.9
Over 40 years.....	55	61.9	15	27.3

B. RELATION TO SEX IN SEVENTY-THREE\* PATIENTS WITH PNEUMONIA DUE TO PNEUMOCOCCUS TYPE III, VII OR VIII

Sex of Patient	Total Series		Circulating Capsular Polysaccharide Present	
	Number of Patients	Percentage	Number of Patients	Percentage
Male.....	51	69.8	8	15.7
Female.....	22	30.2	3	13.6

C. RELATION TO DAY OF DISEASE ON WHICH PATIENT WAS ADMITTED TO HOSPITAL IN EIGHTY-NINE PATIENTS WITH PNEUMONIA DUE TO PNEUMOCOCCUS TYPES III, VII OR VIII

Duration of Disease	Total Series		Circulating Capsular Polysaccharide Present	
	Number of Patients	Percentage	Number of Patients	Percentage
1 to 4 days.....	50	56.3	6	12.0
More than 5 days.....	39	43.7	10	25.4

\* Sixteen patients with one of these types of pneumonia were observed in the original study, chiefly in the ward for male patients, and were excluded from sex incidence study.

TABLE 3.—*Relation of Detectability of Circulating Capsular Polysaccharide, Bacteremia and Mortality in Patients with Pneumococcic Pneumonia Treated with Sulfapyridine, Serum or a Combination of the Two*

	Total No. of Patients	Patients Recovered	Deaths	Mortality, Percentage	
1. No bacteremia; no circulating capsular polysaccharide	98	95	3	3.0	
2. Bacteremia; no circulating capsular polysaccharide	21	18	3	14.3	
3. No bacteremia; circulating capsular polysaccharide	6	2	4	66.7	
4. Bacteremia; circulating capsular polysaccharide	10	4	6	60.0	
	135	119	16	11.8	
All patients with associated bacteremia (2 + 4)	31	22	9	29.0	} R.D.E.* 2.3
All patients with a positive reaction for circulating capsular polysaccharide (3 + 4)	16	6	10	62.5	

\* R.D.E., ratio of difference to its error.

TABLE 4.—*Pertinent Data Concerning Patients with Pneumococcic Pneumonia*

Case No.	Age, Sex, Color	Type of Pneumococcus	Lobe Involved	Blood Culture, Day of Disease Blood Was Taken	Kind	Therapy			Level of Sulfapyridine in the Blood	
						First Dose, Day of Disease	Last Dose, Number of Hours Later	Amount, Gm.	Day of Disease	Concentration of Free Drug, per 100 Cc.
1	51 M 150 lb. W	III	R. L. L.	5th?, 7th, 8th, 9th, 10th —	Sp.	5th	209	66	6th 8th 10th 11th 12th 14th	2.3 5.5 2.5 5.5 5.0 2.8
2	60 F 180 lb. C	III	R. L. L.; L. L. L.	3d + 4th + (525 col.) 5th, 6th, 7th, 9th, 10th —	Sp.	4th  13th	160  88	54  25	79 5th 7th 8th 9th 14th	3.9 6.4 11.8 2.6 12.5
3	45 M 120 lb. W	III	L. U. L.	6th + 9th, contaminated 10th + 11th, 12th, 17th —	Sp.	6th	226	61	7th 8th 10th 11th 12th 13th 14th 17th	2.2 4.1 2.7 6.7 5.3 3.6 2.7 Trace
4	45 F 106 lb. C	III	R. U. L.	8th + (1,540 col.) 9th + 10th, 11th, 12th, 14th, 17th — 20th, 22d —	Sp.	8th  21st  35th	160 (15th day) 216 (29th day) 170 (42d day)	54  48  40	142 10th 11th 12th 14th 22d 26th 30th 39th 41st	8.0 10.2 4.4 7.6 7.8 9.8 2.6 9.0 12.6
5	56 F 150 lb. C	III	R. L. L.; spread to L. L. L.	2d + 6th, 7th, 9th —	Sp. and serum	2d 12th	252 (12th day) 6	102 495,000 U. S. P. units	2d 3d 4th 5th 6th 7th 8th 9th 10th 11th 12th 13th	2.5 4.7 3.6 2.2 2.0 0.0 4.1 5.7 3.4 20.0 14.3 4.9
6	35 M Wt.? C	III	R. L. L.; L. L. L.	1st, 2d, 3d —	Serum	1st	33	700,000 U. S. P. units	0	0
7	54 F Wt.? P. R.	III	R. U. L.; R. L. L.; empyema	Day of disease?; day of admission: 1st + (68 col.); 3d, 5th —	Sp.	Day in hospital 3d	  66	16½	Day in hospital 4th 6th	4.3 1.8
8	47 M 135 lb. W	III	R. L. L.; R. U. L.	3d, 8th, 11th —	Sp. and serum	(a) 3d (b) 6th (c) 11th 3d	44 (5th day) 16 (7th day) 136 (17th day) 29	16 9 32	57 4th 9th 12th 14th 17th	8.2 1.8 4.6 8.5 6.6
								332,500 U. S. P. units		

\* The following abbreviations have been employed: S.S.S., circulating capsular polysaccharide (specific soluble substance); upper lobe of the right lung; L.L.L., lower lobe of the left lung; L.U.L., upper lobe of the left lung; Sp., sulfapyridine; B., ("Blood Culture" column) or a positive result for the procedure in question (in other columns); —, a negative result for the

Serologic Studies				S. S. S. in Urine, Day of Disease	Normal Temperature, Day of Disease	Outcome	Comment
Day of Disease	S. S. S.	AGT.	PPT.				
From 5th to 11th day daily studies	± B. or + B.	—	—	13th + 17th + 25th +	41st	Recovery	Temperature continued elevated during administration of Sp.; convalescence marked by frequent brief elevations of temperature
13th to 17th	± B. to ± P.	—	—				
19th to 44th	—	—	—				
3d	+	—	—		14th	Recovery	Temperature normal on 8th to 11th days; Sp. stopped on 11th day; S.S.S. still present; prompt recurrence of fever; disease controlled by resumption of Sp.
7th	+ B.	—	—				
9th	+ B.	—	—				
11th	± B.	—	—				
14th	± B.	—	—				
19th	+ B.	—	—				
From 6th to 23d day	+ B. or + B.	—	—	11th + 81st —	38th	Recovery	Temperature first lowered beyond 100 on 11th day; occasional rises of temperature to between 100 and 101 until 38th day
27th	± P.	—	—				
41th	±	—	—				
From 10th to 27th	+ B. to +++ B.	—	—	14th + 15th + 21st + 47th + 104th — 136th —	36th	Recovery	Three courses of Sp. required because of recurrence of disease on withdrawal of drug; small collection of fluid and air over R.U.L. throughout course of disease, which material was resorbed slowly and was never aspirated; transfusion 25th day
34th	+ B.	—	—				
35th	+ B.	—	—				
46th	+	—	—				
49th	+++ B.	—	—				
69th	++ P	1/4	—				
81st	+ P.	—	—				
104th	—	—	—				
136th	—	—	—				
2d	—	—	—		Never permanently normal	Death (14th day)	Large doses of Sp. given orally and intravenously; blood Sp. levels low but methemoglobin concentration 25%; three blood transfusions (250 cc.) given; Sp. withdrawn because of drop in white blood cells on 12th day; doses of serum followed by prompt elevation of temperature to 104 and progressive coma
4th	+ P.	—	—				
5th	+ P.	—	—				
7th	+ B.	—	—				
10th	± B	—	—				
13th	—	1/10	1/8				
14th	—	—	—				
1st	—	—	—	2d +	Never	Death (4th day)	Considerable tachycardia and dyspnea on admission; digitalis (22 cat units) given in 15 hr.; pneumonia in lower lobes of both lungs; syphilitic aortitis and fatty degeneration of liver apparent at autopsy
2d	+	1/8	—				
3d	—	1/10	1/4				
Day in hospital 3d	+	1/32	—		Normal on 4th day of hospitalization; rose again on 5th day; elevated until death	Death (8th day of hospitalization)	Patient known to be diabetic for 10 yr.; pneumonia in R.L.L. two months before admission; diabetes difficult to control; small quantities of Sp. taken because of vomiting and withdrawn at time of thoracotomy 4 days ante mortem
4th	—	—	—		Drop to normal within 48 hr. after therapy started; return after cessation of Sp.	Death (17th day)	On 9th and 10th days chest fluid negative for Pneumococcus type III but S.S.S. found; on 12th day culture of chest fluid positive; thoracotomy and rib resection on day of death
6th	—	—	—				
7th	—	—	—				
10th	—	1/32	1/16				
13th	±	1/16	1/16				
17th	± P.	1/16	1/16				
9th	± B.	—	—				
10th	± B.	—	—				
12th	+ B.	—	—				
14th	++ B.	—	—				

AGT., agglutinin; P.P.T., precipitin; R.L.L., lower lobe of the right lung; R.M.L., middle lobe of the right lung; R.U.L., lobe after centrifugation; P., precipitates after centrifugation; +, cultures positive for pneumococci obtained only in broth procedure in question; col., colonies; H.S., horse serum; R.S., rabbit serum; I.V., intravenously, and I.T., intrathecally.

TABLE 4.—*Pertinent Data Concerning Patients with Pneumococcic*

Case No.	Age, Sex, Weight, Color	Type of Pneumococcus	Lobe Involved	Blood Culture, Day of Disease Blood Was Taken	Kind	Therapy			Level of Sulfapyridine in the Blood	
						First Dose, Day of Disease	Last Dose, Number of Hours Later	Amount, Gm.	Day of Disease	Concentration of Free Drug, per 100 Cc.
9	56 M Wt.? C	III	L. L. L.; empyema	Day in hospital 2d — 24th —	Sp.	Day of disease?; day in hospital, 2d	286 (13th day)	67	Day in hospital 3d 5th 7th 10th 12th Chest Fluid 15th	2.0 4.5 3.9 7.4 6.0 10.0
10	54 M 163 lb. C	III	R. L. L.; L. L. L.	6th, not done 7th —	Sp.	7th	31	17	8th	6.5
11	69 M Wt.? C	III	L. U. L.; L. L. L. (no roentgenogram)	5th + (3,408 col.) 6th + ( 125 col.) 7th +	Sp.	5th	44	23	6th 7th	5.4 4.7
12	41 M 190 lb. C	VII	R. L. L.	3d —	Sp. and serum	(a) 4th (b) 11th 4th	67 (7th day) One dose	23 } 28 5 } 152,000 units	5th 7th	4.2 6.2
13	62 M Wt.? W	VII	L. L. L. (no roentgenogram)	8th, not done 9th + (3,225 col.) 10th + ( 41 col.) 11th, 12th, 13th, 14th —	Sp.	9th	132 (15th day)	49	10th 12th 13th 14th 15th	3.1 3.2 4.5 5.0 5.9
14	61 M Wt.? C	VII	R. U. L.; R. M. L.(?)	3d, 4th, 5th, 6th, 7th — 11th + (innumerable col.) 12th + (532 col.) 13th, 15th, 16th — 22d, 27th, 32d — 58th + (9 col.) 61st, 63d, 64th — 72d, 74th, 77th —	Serum and	(a) 3d	59 H. S. 304,000 units R. S. 990,000 units	13th 15th 17th 1,294,000 units 19th 8 R. S. 500,000 units 33d 44 R. S. 540,000 units 36th I. V. 63d 65,000 units 65th I. T. (62d day) 67th 24 R. S. 130,000 units 69th	6.2 9.3 7.4 4.0 9.6 12.4 3.5 10.3 6.3 6.4	
					Sp.	(a) 12th (b) 32d (c) 58th	204 (21st day) 124 (37th day) 432 (76th day)	64 } 236 34 } 138 }	72d 74th 76th 77th	11.0 11.6 5.9 10.0
									Spinal Fluid	
									61st 62d 64th 65th 66th 67th 69th 71st 72d 74th 75th	2.2 4.6 5.8 5.4 3.6 4.7 2.6 8.1 6.6 9.0 5.6
									Urine	
									77th	80.0
15	43 M 160 lb. C	VIII	R. L. L.; R. M. L.(?)	1st + (60 col.) 3d, 7th, 27th —	Sp. and serum	1st 1st	44 46	14 186,400 units	3d	9.2
16	51 F Wt.? C	VIII	R. U. L.	2d, not done 3d + (innumerable col.) 4th + 5th +	Sp.	3d	47	38	a.m. 4 p.m. 4 5	Trace 1.4 19.5

Serologic Studies				S. S. S. in Urine, Day of Disease	Normal Temperature, Day of Disease	Outcome	Comment
Day of Disease	S. S. S.	AGT.	PPT.				
Day in hospital							
5th	+ B.	—	—	12th +	Normal from 4th to 15th day of hospitalization; rise to 102 F. on 16th day; operation on 18th day; normal for 3 days; irregular rises until death	Death (27th day of hospitalization)	Type III pneumococcus pneumonia in R.L.L. 8 weeks before final admission; prompt response to Sp. at that time; history for the 6 weeks before final admission not obtainable; patient severely dyspneic on admission from extensive empyema; S.S.S. and viable organisms always contained in chest fluid (see text)
6th	+ B.	—	—				
7th	++ B.	—	—				
9th	+ B.	—	—				
12th, 14th, 16th	+ B.	—	—				
19th	± P.	—	—				
20th	+ B.	—	—				
22d	± P.	—	—				
25th	± B.	—	—				
26th	±	—	—				
7th	++ B.	—	—		Never	Death (9th day)	
6th	++++ B.	—	—		Never	Death (7th day)	Number of circulating bacteria diminished under Sp. therapy, with slight fall of temperature but no clinical improvement
7th	++++ B.	—	—				
3d	± B.	—	—	8th —	5th day (12 hr. after onset of therapy)	Recovery	
9th	—	1/32	1/8	14th —			
14th	—	1/16	—				
17th	—	—	—				
9th	+ B.	—	—		Never	Death (15th day)	Extra large doses of Sp. given because of poor clinical response; condition progressively worse; death despite loss of detectable S.S.S. from blood and appearance and progressive increase of agglutinins
10th	± B.	—	—				
11th	—	—	—				
12th	—	1/4	—				
13th	—	1/8	—				
14th	—	1/16	—				
12th	+	—	—	55th +	3d -12th day-elevated 13th-21st day-normal 22d -33d day-elevated 34th-41st day-normal 42d -44th day-slightly elevated 45th-48th day-normal 49th-58th day-progressively elevating, culminating in chill 58th-63d day-spiking 64th-65th day-normal 66th day -elevated 67th day -normal 68th-69th day-elevated 70th-71st day-normal 72d -death -progressive rise in temperature	Death (78th day)	Fatal type VII pneumococcus meningitis; strain became sulphyridine fast terminally
13th	++	1/8	1/8				
19th	+	1/32	1/4				
22d	—	—	1/4				
20th	—	—	—				
27th	±	—	—				
30th	+	1/8	—				
32d	++	1/4	—				
33d	+	—	1/2				
35th	—	—	—				
38th	—	1/4	—				
40th	+	1/8	—				
43d	+	1/8	—				
45th	—	1/16	—				
50th	—	—	—				
54th	—	—	—				
58th	—	—	—				
61st	—	1/4	—				
62d	—	1/32	1/16				
65th	—	1/64	1/8				
69th	Spinal Fluid	1/2	—				
71st	—	1/2	—				
72d	—	—	—				
60th day +							Cultures of Spinal Fluid 59th day + (45,000 cells) 60th day + 62d day + 63d, 65th, 66th, 69th, 70th days,— 71st day + 74th day + 75th day + (2,800 cells) 76th day —
62d day +							
63d, 65th, 66th, 69th, 70th days,—							
71st day +							
74th day +							
75th day + (2,800 cells)							
76th day —							
After Serum							
2d	+ B.	1/16	1/16	4th —	Normal 3d to 6th day; slight rise; pleural effusion; slow return to normal	Recovery	
3d	± P.	1/64	1/16	11th +			
4th	—	1/64	1/16				
8th	—	1/8	1/4				
10th, 18th, 16th, 23d	—	—	—				
3d	+ P.	—	—	4th +	Normal first 24 hr. in hospital and again on 5th day for 24 hr.	Death (6th day)	
4th	++++ B.	—	—				
5th	+++ B.	—	—				

patients whose reaction for circulating capsular polysaccharide was positive were in this group. The remaining 10 (62.5 per cent) of the patients were in the group admitted after the fourth day of the disease (table 2 C).

*Relation of Circulating Capsular Polysaccharide, Bacteremia and Mortality.*—Among the 135 patients the mortality was 11.8 per cent. It was lowest (3 per cent) in the 98 patients with neither bacteremia nor capsular polysaccharide in the blood (table 3) and was approximately five times as great (14.3 per cent) among the 21 patients who had bacteremia but in whose blood capsular polysaccharide was not detected. The mortality among the 16 patients with circulating capsular polysaccharide was 62.5 per cent; only 6 of these 16 patients recovered. Among the 31 patients with bacteremia, with or without circulating capsular polysaccharide in the blood the mortality was 29 per cent. Among the 16 patients with capsular polysaccharide in the blood, with or without bacteremia, the mortality was 62.5 per cent.

Further separation of patients with a positive reaction for circulating capsular polysaccharide into those with and those without bacteremia yielded groups which were too small to permit statistically valid analysis. There was, however, no tendency for the mortality rates to be altered.

*Description of Patients in Whose Blood Capsular Polysaccharide Was Found.*—A detailed analysis of the cases of the 16 patients in whom blood capsular polysaccharide was found is given in table 4. Treatment was rotated after the type of pneumococcus had been determined in the sputum, irrespective of the presence of capsular polysaccharide in the blood. Ten of the patients with polysaccharide in the blood received sulfapyridine alone, 5 received serum and sulfapyridine and 1 received serum alone.

Patients Treated with Sulfapyridine Alone (cases 1, 2, 3, 4, 7, 9, 10, 11, 13 and 16; table 4): Of the 10 patients treated with sulfapyridine alone, 6 died (cases 7, 9, 10, 11, 13 and 16) and 4 recovered (cases 1, 2, 3 and 4).

Patients Treated with Sulfapyridine Alone Who Died: Three patients (cases 10, 11 and 16) with uncomplicated pneumonias received sulfapyridine continuously to the time of death; after a total of 17 to 38 Gm. of sulfapyridine was taken all had blood levels of the drug generally considered satisfactory (2 to 8 mg. per hundred cubic centimeters). These patients died after two and in less than four days of hospitalization, on the ninth, seventh and sixth day of the disease, respectively. Two of the patients (cases 10 and 11) showed no evidence of clinical improvement, although the number of organisms in the blood





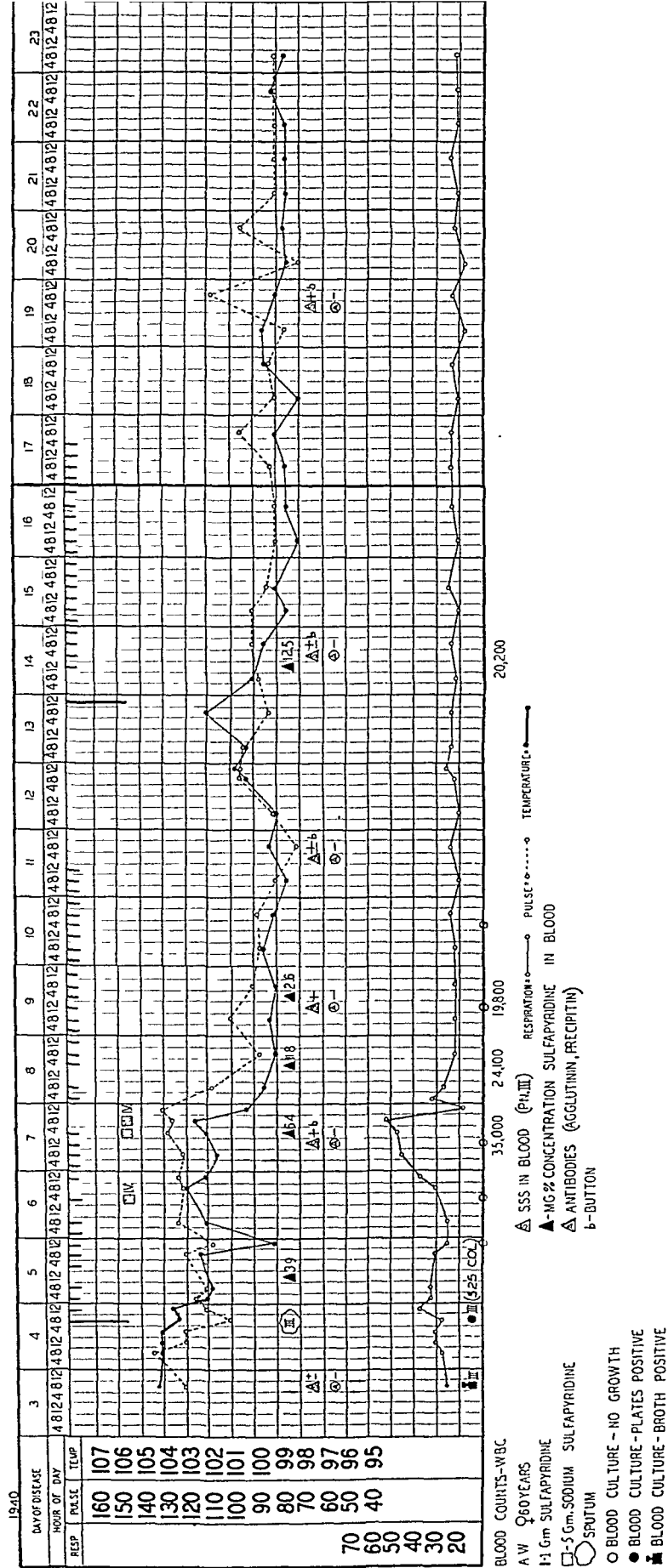
of the onset of the disease obtainable. The first of these (case 7), who had bacteremia on admission, had been known to be diabetic for ten years, and the diabetes was controlled with difficulty during her stay in the hospital. She received 16.5 Gm. of sulfapyridine during the first sixty-six hours in the hospital and had a level of 4.3 mg. of the drug per hundred cubic centimeters of blood. Administration of sulfapyridine was stopped after rib resection, and the patient became progressively worse and died. The second patient (case 9) had been discharged from the hospital (eleven weeks before the final admission) after recovery from type III pneumococcus pneumonia treated with sulfapyridine. Because of the severity of his illness and the intensity of dyspnea on readmission, a history of the interval could not be obtained. A total of 67 Gm. of sulfapyridine was given during the next eleven and one-half days, which resulted in a level of 7.4 mg. of the drug per hundred cubic centimeters of blood and a level of 10 mg. per hundred cubic centimeters of chest fluid. Despite continuation of therapy, the chest fluid continued to yield type III pneumococci on culture and contained considerable amounts of circulating capsular polysaccharide on all examinations. Large quantities of pus were removed on two occasions, and the temperature reached normal. Three days after cessation of therapy with sulfapyridine the temperature became elevated, and two days later a rib resection was done, after which the patient, despite irregular rises of temperature, improved. Throughout this period, and up to the day before death, capsular polysaccharide was detectable in the blood, and cultures of material from the wound continued to yield pneumococci of type III. Antibodies were never detected in the blood. On the twenty-seventh day the patient died suddenly; permission for a post-mortem examination was not obtained.

**Patients Treated with Sulfapyridine Alone Who Recovered:** The course of the disease in the 4 patients who recovered under treatment with sulfapyridine alone (cases 1, 2, 3 and 4) was characterized by a prolonged fever which subsided slowly during administration of the drug (fig. 3) or recurred promptly when the drug was discontinued (fig. 4). The capsular polysaccharide remained in the blood for many days; either a slight amount of antibody appeared later or there was none at all. In cases 2 and 4 several courses of therapy with sulfapyridine were given, and in case 4<sup>7</sup> capsular polysaccharide was detectable in the blood for at least eighty-one days.

**Patients Treated with Serum and Sulfapyridine:** Of the 5 patients (cases 5, 8, 12, 14 and 15) treated with serum and sulfapyridine, 3 (cases 5, 8 and 14) died and 2 (cases 12 and 15) recovered.

**Patients Treated with Serum and Sulfapyridine Who Died:** In 2 of the 3 cases with a fatal outcome, treatment with serum and with





because capsular polysaccharide was present in the blood specific serum was administered. In all, 495,000 U. S. P. units of refined and concentrated rabbit antipneumococcus serum was administered. The capsular polysaccharide disappeared and a moderately high titer of antibodies appeared in the blood. The temperature rose again; the patient became stuporous and died forty-eight hours later.

In case 14 the patient was originally in the group treated with serum. After 1,294,000 U. S. P. units of therapeutic horse and rabbit antipneumococcus serum alone had failed to control the disease and the patient appeared to be moribund, he was given serum and sulfa-pyridine simultaneously. Capsular polysaccharide was present in the

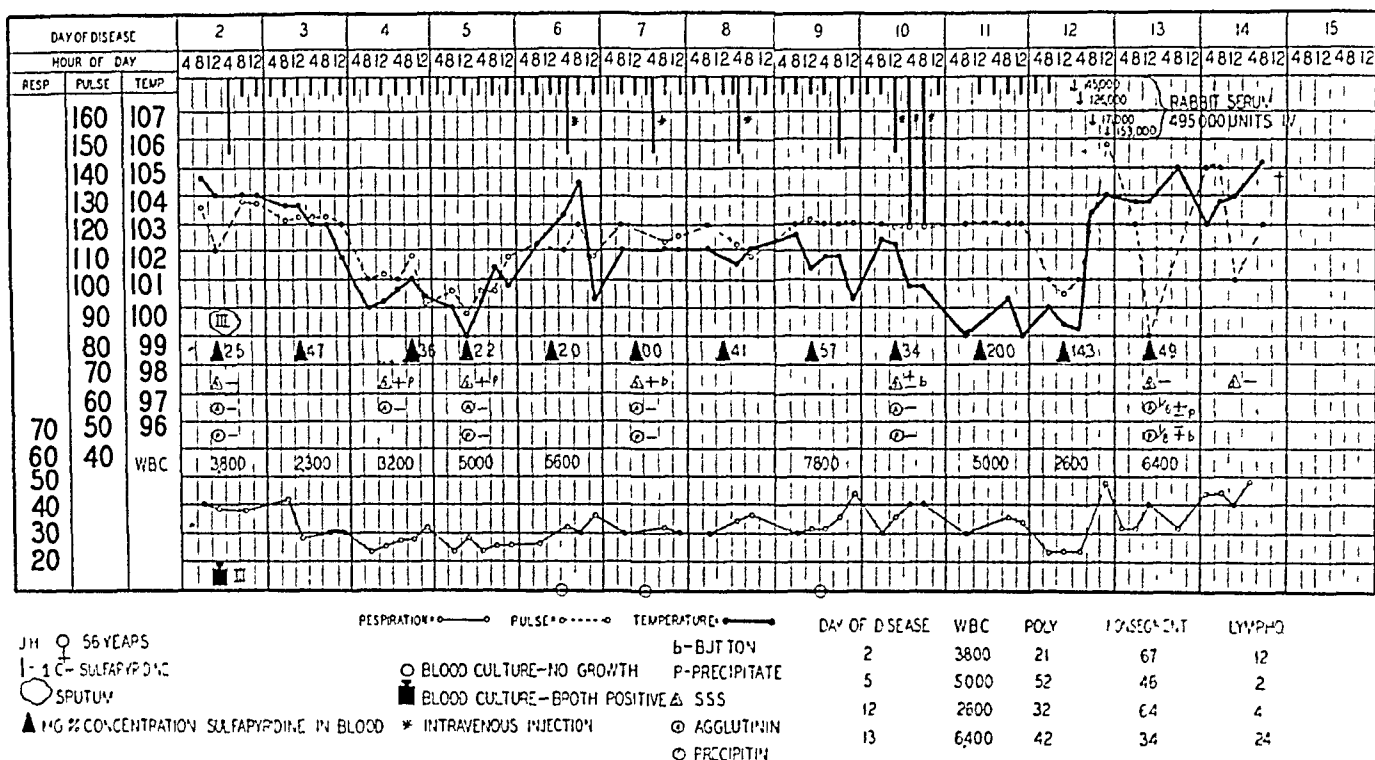


Fig. 5 (case 5).—Course of illness and presence of circulating capsular polysaccharide (S. S. S.).

blood at this time and persisted for at least eight days (precipitin was also present in the blood), then disappeared as the patient's clinical condition improved.<sup>7</sup> On several occasions after cessation of treatment, capsular polysaccharide reappeared in the blood and was associated with recrudescence of the fever. On each occasion the capsular polysaccharide disappeared from the blood, and the fever subsided when administration of the drug was resumed. Finally, meningitis developed, which did not respond to administration of both drug and serum; the strain of pneumococci had become sulfapyridine fast. The patient died on the seventy-eighth day of disease.



thirteenth day of disease and was present simultaneously with precipitin and agglutinin for at least five days.<sup>7</sup> The patient remained severely ill; thoracotomy and rib resection were performed on the seventeenth day of disease, and he died that day.

**Patients Treated with Serum and Sulfapyridine Who Recovered:** The 2 patients (cases 12 and 15) who recovered under treatment with serum and sulfapyridine made the most satisfactory responses of the entire series. In both patients circulating capsular polysaccharide was present on admission, and both received a relatively small total quantity of serum and sulfapyridine simultaneously. There was prompt disappearance of the polysaccharide from the blood and equally prompt appearance of antibody, these being simultaneously present in case 15.<sup>7</sup>

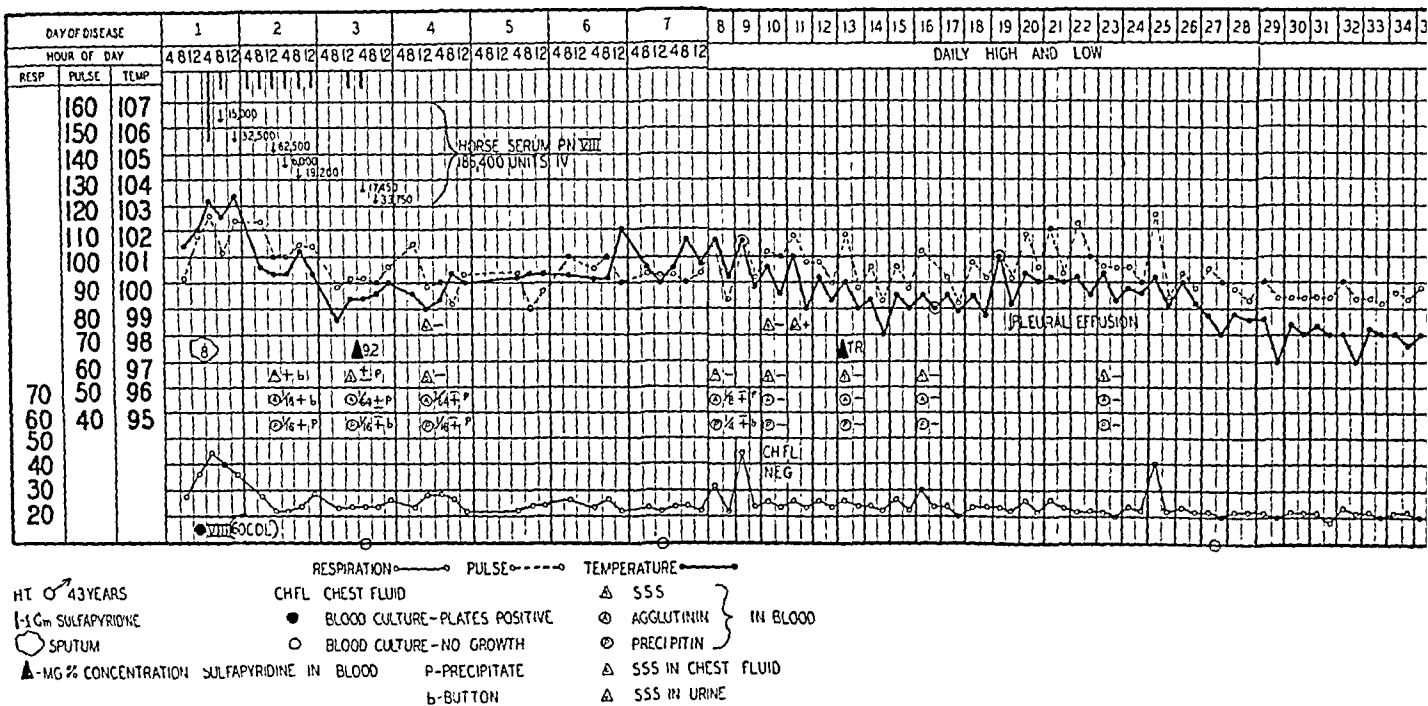


Fig. 7 (case 15).—Course of illness and presence of circulating capsular polysaccharide (S. S. S.).

The temperature fell in case 12 within twelve hours after initiation of therapy and remained normal thereafter. The convalescence in case 15 (fig. 7) was complicated by the development of a sterile pleural effusion. The temperature was slightly elevated during the pleural effusion and became normal when the fluid was absorbed.

**Patient Treated with Serum Alone:** The sixteenth patient (case 6) whose serum gave a positive reaction for capsular polysaccharide received only serum. This patient died despite rapid neutralization of circulating capsular polysaccharide and the presence of antibodies in the blood. Capsular polysaccharide was first detected after intravenous administration of therapeutic antipneumococcus serum.

## COMMENT

The incidence in the entire series of cases in which there was a positive reaction for circulating capsular polysaccharide was 11.8 per cent (table 1); however, among the cases of pneumonia due to *Pneumococcus* type III, VII or VIII alone the incidence was 17.9 per cent. Capsular polysaccharide in the blood in cases of pneumonia due to one of these types is not infrequent.

It is apparent that the type of the infecting pneumococcus, the age of the patient and the duration of disease before treatment is initiated are factors which influence the appearance of capsular polysaccharide. In the present series the polysaccharide was not detected in the blood of patients with type I pneumococcus pneumonia<sup>8</sup> and occurred in more than one quarter of the patients with type III pneumococcus pneumonia. In patients with pneumonia due to the type VII or VIII pneumococcus (table 1), it appeared less frequently, in approximately 10 per cent. It also occurred in patients with pneumonia due to *Pneumococcus* type XI, XX or XXXIII and among patients studied less systematically later with pneumonia caused by *Bacillus Friedländer A*. Pneumococci of type III form large capsules and produce large quantities of capsular polysaccharide as compared with pneumococci of type I. The poorer response of infections caused by the type III pneumococcus to serum therapy, as compared with the responses of infections due to the type I or type VII pneumococcus and some other organisms may be due to this characteristic. It is also possible that the carbohydrate of *Pneumococcus* type III is less firmly bound to the organism than are the carbohydrates of other types of pneumococci. Since the studies of Cole<sup>9</sup> on infected exudates and serums of patients with pneumococcal pneumonia it has been known that circulating capsular polysaccharide neutralizes antibody in vitro, and Downie<sup>10</sup> demonstrated the neutralization of antibody by capsular polysaccharide in vivo. The occurrence of neutralization of antibody by capsular polysaccharide is suggested in case 8 of the present series. This patient received 332,500 U. S. P. units of antipneumococcus rabbit serum type III on the third and fourth days of disease. Antibodies were first detected on the tenth day of disease, a fact which suggested either that the antibody was autogenous,

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8. Park and Cooper detected traces of a "specific toxic substance" (believed to be soluble specific substance neutralized by antibody) in the late toxic stage of 4 cases of type I pneumococcus infections (Bullowa, J. G. M.: *Lobar Pneumonia and Its Treatment with Refined Sera*, in Alexander, J.: *Colloid Chemistry*, New York, The Chemical Catalog Company, 1928, vol. 2, p. 793).

9. Cole, R. I.: *Neutralization of Antipneumococcus Immune Bodies by Infected Exudates and Sera*, *J. Exper. Med.* **26**:453, 1917.

10. Downie, A. W.: *Experiments with Type-Specific Pneumococcus Polysaccharides in Rabbits*, *J. Path. & Bact.* **45**:149, 1937.

and not the one introduced, or that it had been liberated from capsular polysaccharide at the time it was detected. Capsular polysaccharide was not detectable in the blood during this period, though the pleural fluid contained large amounts of the substance on the ninth and tenth days of disease. Both these fluids were sterile on culture. In Finland's<sup>11</sup> experience, capsular polysaccharide was not detectable in fluid from sterile pleural effusions. Diffusible substances in the blood appear in greater concentration in an area of inflammation. It is probable, therefore, that capsular polysaccharide was present in the blood in case 8 in subdetectable quantities and was concentrated in the inflamed pleural cavity. The subdetectable amount of circulating capsular polysaccharide may have been sufficient to neutralize the injected antibody. Larger and detectable quantities of circulating capsular polysaccharide will neutralize larger amounts of antibody.

The second factor, the age of the patient, appears to be of considerable importance in conditioning the appearance of capsular polysaccharide in the blood. This relation is demonstrated by the data in table 2 A, which indicate a significantly greater incidence in the older age group of cases in which there was a positive reaction for circulating capsular polysaccharide.

The third factor, duration of disease, seems to be of less importance than the age of the patient, although there is some indication that the incidence of capsular polysaccharide in the blood is greater in those admitted to the hospital after the fourth day of their disease (table 2 C). An analysis of the cases of type III pneumococcus pneumonia alone, however, shows no significant difference in the incidence of capsular polysaccharide in the early and in the late stages of infection (among 20 cases of the early stage—first to fourth day—there were 5 in which the reaction for capsular polysaccharide was positive; among 20 cases of the late stage—fifth day or later—there were 6 in which the reaction was positive).

The increased fatality rate associated with the presence of capsular polysaccharide in the blood of patients with pneumococcic pneumonia is clearly indicated in table 3. The mortality for the whole series was 11.8 per cent, a figure similar to the mortality rate of a large reported series of cases of treated pneumococcic pneumonias.<sup>12</sup> In the presence of bacteremia the mortality rose to 29 per cent, while in the presence of circulating capsular polysaccharide 62.5 per cent of the patients died.

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11. Finland, M.: Immunological Reactions of Pneumonic Pleural Fluids, *J. Exper. Med.* **55**:169, 1932.

12. Lord, F. T.; Robinson, E. S., and Heffron, R.: *Chemotherapy and Serum Therapy of Pneumonia*, New York, Commonwealth Fund, Division of Publications, 1940, chap. 8, p. 62.



Cohn and Lewis<sup>13</sup> found that the fatality rate increased in relation to the number of lobes involved. In their cases involvement of four lobes was associated with a mortality of 68.2 per cent, while there was a 40.7 per cent mortality when only three lobes were involved. The increased fatality rate in cases in which there was a positive reaction for circulating capsular polysaccharide is not correlated with the number of lobes involved, because in 7 patients only one lobe was affected; two lobes were affected in the remaining 9, and there was none with more than two pneumonic lobes. Corresponding figures reported by Cohn and Lewis were 8.5 per cent for cases in which one lobe was involved and 24.5 per cent for cases in which two lobes were involved.

Spring, Lowell and Finland<sup>14</sup> demonstrated that the growth inhibition and pneumococidal action of sulfapyridine in vitro is not affected by the addition of capsular polysaccharide. Accordingly, mechanism by which capsular polysaccharide increases fatality must be sought in the effect of that substance on the immune mechanisms important for recovery. Early observations by Rosenow<sup>15</sup> and by Tchistovitch and Yourevitch,<sup>16</sup> confirmed and extended by a number of other workers,<sup>17</sup> demonstrated that capsular polysaccharide was specifically antiopsonic and therefore specifically inhibited phagocytosis. Rosenow<sup>15</sup> and Felton and Bailey<sup>18</sup> have demonstrated that capsular polysaccharide specifically makes avirulent pneumococci virulent and augments the virulence of virulent organisms. The effectiveness of sulfapyridine in control of pneumococcal infections is the result of the combined bacteriostatic activity of the drug and of the immune substances which develop during

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13. Cohn, A. F., and Lewis, W. H.: Lobar Pneumonia and Digitalis, *Am. J. M. Sc.* **189**:457, 1935.

14. Spring, W. C.; Lowell, F. C., and Finland, M.: Studies on the Action of Sulfapyridine on Pneumococci, *J. Clin. Investigation* **19**:163, 1940.

15. Rosenow, E. C.: Human Pneumococcal Opsonin and the Antiopsonic Substance in Virulent Pneumococci, *J. Infect. Dis.* **4**:285, 1907.

16. Tchistovitch, N., and Yourevitch, V.: Sur les opsonines et les antiphagines dans l'infection pneumococcique, *Ann. Inst. Pasteur* **22**:611, 1908.

17. Wadsworth, A. B., and Sickles, G. M.: The Effect of Type I Pneumococcus Culture Broth on the Phagocytic Action of Type I Pneumococcus Serum, *J. Immunol.* **14**:321, 1927. Sickles, G. M.: Further Observations on the Effect of Type I Pneumococcus Culture Broth on the Phagocytic Action of Type I Pneumococcus Serum, *ibid.* **14**:329, 1927. Sia, R. H. P.: Studies on Pneumococcus Growth Inhibition: VI. The Specific Effect of Pneumococcus Soluble Substance on the Growth of Pneumococci in Normal Serum—Leucocyte Mixtures, *J. Exper. Med.* **43**:633, 1926. Ward, H. K.: Observations on the Phagocytosis of the Pneumococcus by Human Whole Blood: I. The Normal Phagocytic Titre, and the Antiphagocytic Effect of the Specific Soluble Substance, *ibid.* **51**:675, 1930.

18. Felton, L. D., and Bailey, G. H.: Biologic Significance of the Soluble Specific Substances of Pneumococci, *J. Infect. Dis.* **38**:131, 1926.

the course of the disease. Reichel's<sup>19</sup> observations indicate that immune bodies may exert their effects early in the course of an experimental pneumococcic infection, since the serums of rabbits already exhibit specific bacteria-clearing properties one hour after the intravenous inoculation of living pneumococci. An increase of capsular polysaccharide in the blood of patients with pneumococcic pneumonia may be accompanied by "neutralization" of antibodies. Furthermore, Tunnicliff<sup>20</sup> showed that sulfapyridine promotes phagocytosis in plain broth but not in dextrose broth cultures of pneumococci. She suggested that this may be related to an increased concentration of capsular polysaccharide in the dextrose broth cultures as compared with the concentration in plain broth cultures.

It is suggested that specific antibody be administered to those patients in whom circulating capsular polysaccharide is detected so that the anti-immune effects of the latter may be neutralized.

#### SUMMARY

Systematic determination of capsular polysaccharide, agglutinin and precipitin titers were made on samples of blood of 135 patients with pneumonia caused by pneumococci of types I (32 cases), II (4 cases), III (40 cases), IV (1 case), V (9 cases), VII (33 cases) and VIII (16 cases) in a series rotated for treatment with sulfapyridine, with serum or with the two in combination.

Capsular polysaccharide was detected in the blood of 16 patients, or 11.8 per cent of the entire series. Eleven of the 16 had type III, 3 had type VII and 1 had type VIII pneumococcus pneumonia.

There was a significantly greater incidence of positive reactions for circulating capsular polysaccharide in the older age group, a tendency to greater incidence with increasing duration of disease and an equal sex incidence.

The mortality for the patients in whose blood capsular polysaccharide was present was 62.5 per cent, while the mortality for all the patients with bacteremia was only 29 per cent and the mortality for the entire series was 11.8 per cent. The mortality for the patients without bacteremia and without capsular polysaccharide in the blood was only 3 per cent.

Of the 10 patients whose serum gave a positive reaction for capsular polysaccharide and who were treated with sulfapyridine alone, 6 died. The illness of the 4 patients recovering under sulfapyridine therapy

19. Reichel, H. A.: Studies on Pneumococcal Immunity, Proc. Staff Meet., Mayo Clin. **14**:636, 1939.

20. Tunnicliff, R.: Effect of Sulfapyridine on Phagocytosis and Dissociation, J. Infect. Dis. **66**:148, 1940.

alone ran a prolonged course, with a tendency to recurrence of fever, slow disappearance of capsular polysaccharide from the blood and failure to produce antibody.

Of the 5 patients whose serum gave a positive reaction for capsular polysaccharide and who were treated with both sulfapyridine and serum, 3 died; 2 of these did not receive serum and sulfapyridine simultaneously, while the third received insufficient sulfapyridine. The 2 patients recovering after simultaneous serum and sulfapyridine therapy made much more satisfactory clinical responses. The sixteenth patient in whose blood capsular polysaccharide was detected died after treatment with serum alone.

The influence of capsular polysaccharide on the clinical course of illness in these patients is discussed.

Miss Ruth Mayer assisted in the titrations of capsular polysaccharide and of antibodies on most of the patients.

Miss Constance Lehair and Miss Evelyn Greenbaum assisted in the preparation of the manuscript.

# RETINAL ARTERIOVENOUS NICKING

## RELATION TO ENLARGEMENT OF THE HEART IN AMBULATORY PATIENTS WITH HYPERTENSION

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When you cannot measure, your knowledge is meager and not satisfactory.  
—Lord Kelvin.

There are a number of changes visible in the retinal arteries and veins of patients with early or late hypertension. The most frequent are narrowing of the arteries (spasm), changes in caliber (so-called spasm or atheroma), tortuosity, mottling of the arterial reflex, "silver wire" arteries and arteriovenous nicking. We have chosen the last of these lesions for study because (1) arteriovenous nicking is easily and accurately identified after one has sufficient practice, (2) it is the most constant change present in all forms of long-standing hypertension and (3) it never occurs except in patients who have or have had hypertension. Wagener has stated that "spasm" never occurs except in hypertensive patients. Our experience has confirmed this repeatedly, but the phenomenon is largely confined to patients with exceedingly high diastolic pressure (so-called malignant hypertension) and consequently is not commonly seen. This lesion (spasm) has no relation to the size of the heart or the duration of the disease but is important in diagnosis.

Arteriovenous nicking (fig. 1) was first described by the English ophthalmologist Gunn<sup>1</sup> late in the nineteenth century (1883). O'Hare and Walker,<sup>2</sup> in 1922, pointed out that this lesion, along with changes in caliber in the retinal arteries, was present in their arteriosclerotic patients who had hypertension but not in the nonhypertensive patients.

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From the cardiac clinics of Baylor University and Parkland Hospital.

1. Gunn, R. M.: Peculiar Appearance of the Retina in the Vicinity of the Optic Disk Occurring in Several Members of the Same Family, *Tr. Ophth. Soc. U. Kingdom* 3:110, 1883.

2. O'Hare, J. P., and Walker, W. G.: Arteriosclerosis and Hypertension, *Arch. Int. Med.* 33:343 (March) 1924.

It was at first believed that the lesion was produced by the pressure of the hypertensive artery on the vein, but this was none too logical, since the lesion persisted after the pressure had fallen to normal. Moreover, Friedenwald,<sup>3</sup> in 1929, showed that the lesion was really a fibrotic change at the crossing of the artery and the vein. It is for this reason that we use the term arteriovenous nicking instead of arteriovenous compression. A better term would be arteriovenous fibrosis. It is now generally agreed that this phenomenon occurs only in hypertensive patients (Thiel,<sup>4</sup> Volhard,<sup>5</sup> Wagener,<sup>6</sup> and others). In our combined experience with

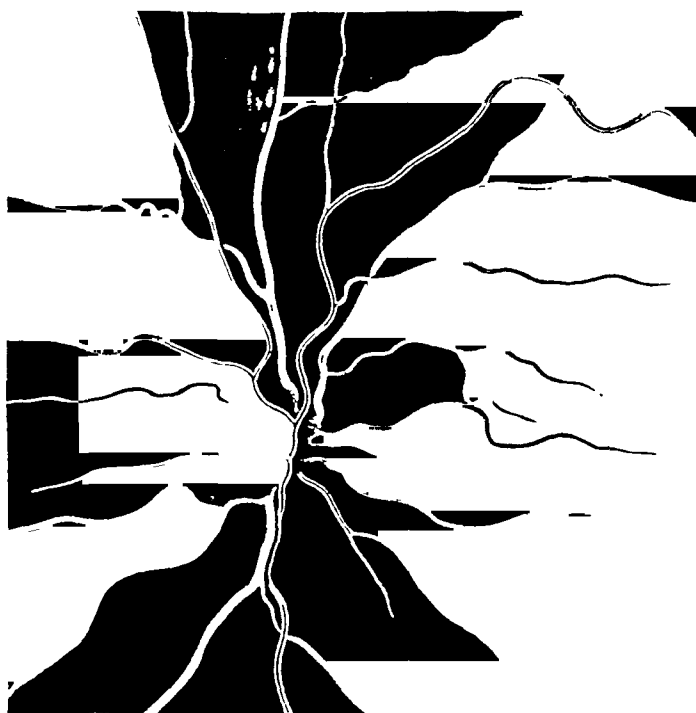


Fig. 1.—The first drawing of the lesions of the retinal arteries and veins designated as arteriovenous nicking (reproduced from Gunn<sup>1</sup>).

hospital, clinic and private patients during the past ten years, we have found no exceptions to this rule. One must be most careful to distinguish

3. Friedenwald, J. S.: *The Pathology of the Eye*, New York, The Macmillan Company, 1929.

4. Thiel, R.: Significance of Examination of the Eyes for the Diagnosis and Differential Diagnosis of Hypertension and Kidney Diseases, *Klin. Wchnschr.* **15**:1785 (Dec. 5) 1936.

5. Volhard, F.: The Significance of the Examination of the Eyes for the Understanding of Hypertension and Kidney Diseases, *Klin. Wchnschr.* **15**:1745 (Nov. 28) 1936.

6. Wagener, H. P.: The Clinical Interpretation of Retinal Vascular Lesions in Hypertension, *Pennsylvania M. J.* **40**:705 (June) 1937.

between slight compression of the vein by the artery and definite arteriovenous nicking (fig. 2). Slight compression may be found in persons who have never had hypertension. This distinction is discussed more fully in subsequent paragraphs of this paper.

For some years it has been obvious to us, and doubtless to many others, that there must be a close relation between this phenomenon and enlargement of the heart in hypertensive states, since both signs appear late in the course of the disease. This research was undertaken

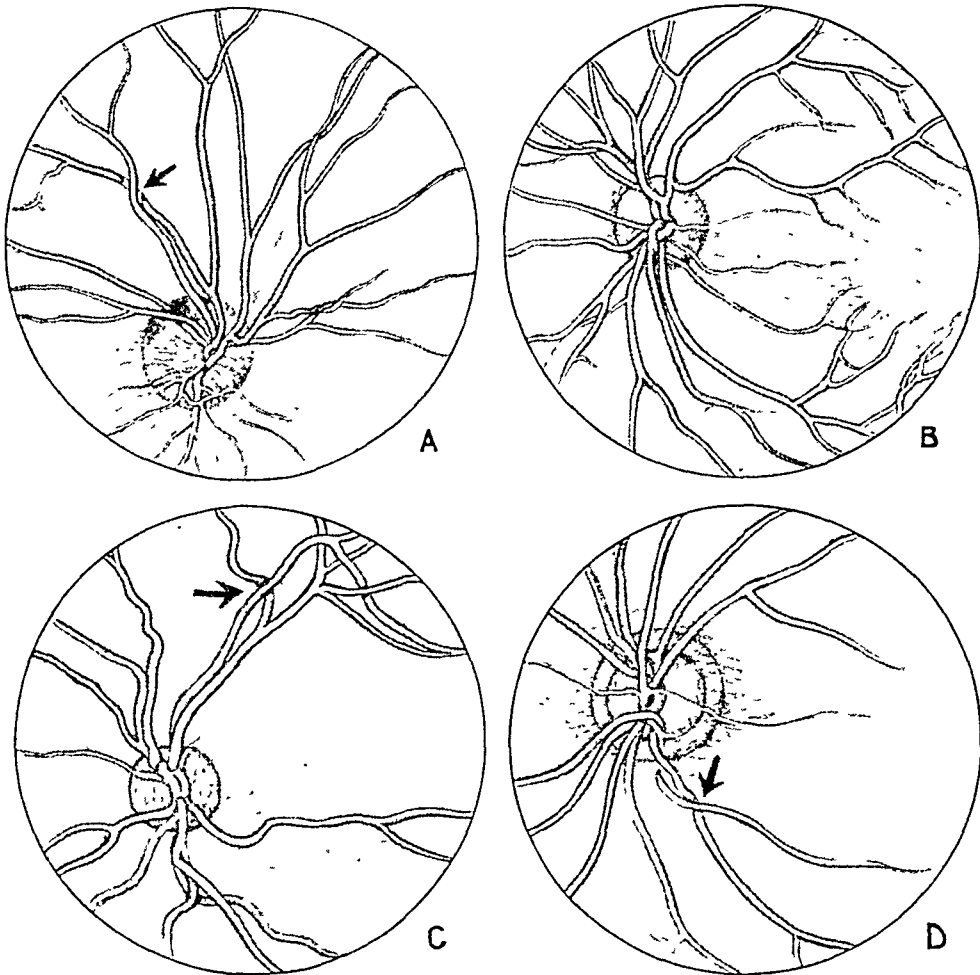


Fig. 2.—The degrees of arteriovenous nicking. *A*, definite; *B*, none (normal retinal arteries and veins); *C*, early, and *D*, moderate.

to determine as precisely as possible the exactness of this relation. In order to secure the greatest accuracy in the retinal examinations one person (S. A. S.) did all the examining, through dilated pupils only. The greatest difficulty, however, was encountered in the determination of the presence of enlargement of the heart. We feel that by applying the same rules of measurement and the same roentgenologic technic in each case and comparing the various subgroups with each other, we have,

with fair satisfaction, overcome this obstacle. It remains, however, the *bête noire* in all studies of this sort and for that reason is discussed more adequately in subsequent paragraphs.

### METHOD

All the patients (317) included in this study were ambulatory and were in the private practice of one of us (S. A. S.) or were attending the cardiac clinics (table 1). Each patient's history was carefully obtained and the physical examination carefully made, the data being recorded on a form similar to that recommended by the American Heart Association. A careful retinal study was made by one of us (S. A. S.) before the heart was examined. A teleroentgenogram and an electrocardiogram were made for each patient, as well as a urinalysis and a Kline test. Other examinations were made when indicated.

TABLE 1.—*The Distribution According to Age, Sex, Average Blood Pressure and Race of Three Hundred and Seventeen Patients with Hypertension*

Average age, years.....	53.7	
Lowest.....	27	
Highest.....	82	
	Number	Percentage
Females.....	176	55.5
Males.....	141	44.5
Average Blood Pressure, Mm. Hg.		
Systolic.....	192	
Diastolic.....	114	
	Number	Percentage
Colored patients.....	150	47.4
White patients.....	167	52.6

### RETINAL EXAMINATION

Each branch of the retinal artery was examined out to the finest terminals in each eye. If the vessels could not be seen because of cloudy media the patient was not included. It became obvious early in our experience that there were various degrees of arteriovenous nicking and the significance of the early changes was far different from that of the well developed lesion. We arbitrarily chose the following designations and recorded them as such on the patient's chart on the first examination: (1) early arteriovenous nicking, (2) moderate arteriovenous nicking and definite arteriovenous nicking (fig. 2). Later we found that Thiel, in Frankfort on the Main, recognized the vital necessity of making similar distinctions.

After one examines many retinal arteriovenous crossings it becomes clear that in the normal person there is no change in appearance of the veins at the crossing. In some cases the vein is slightly compressed or exhibits a U-shaped deformity caused by being pushed aside, but on close examination no area of obliteration of the vein is visible on either

side of the artery (fig. 2 *B*). We have designated this lesion early arteriovenous nicking. It may be found in patients who never have had hypertension, but it is vastly more common in hypertensive than in non-hypertensive people; for this reason we suggest that it is an early stage in the development of definite arteriovenous nicking. We have observed such lesions develop in 1 patient, over a period of five years, into definite arteriovenous nicking.

Fully developed arteriovenous nicking is accompanied by complete obliteration of the vein on both sides of the artery and is easy to identify (fig. 2 *A*). Partial obliteration of the vein or obliteration on only one side we termed moderate arteriovenous nicking. We have never seen such a lesion in nonhypertensive persons, but of course we cannot be as assured that it is pathognomonic of hypertension as we are that definite arteriovenous nicking is. We take this occasion to warn that crossings within one disk diameter of the optic disk must not be used, for not infrequently the vein dips deep into the retina in this region and gives the appearance of arteriovenous nicking. We have seen the latter phenomenon in many normal persons.

#### DETERMINATION OF THE SIZE OF THE HEART

Teleroentgenograms were made for every patient and the shape of the heart was carefully considered, but since the latter is not amenable to exact measurement we relied largely on comparison of the transverse diameter of the heart with the predicted transverse diameter from the tables of Ungerleider and Clark. These predictions are based on height and weight. We also determined the predicted transverse diameters by the tables of Hodges and Eyster, using the monogram in the book by Kurtz entitled "Orthodiascopy."<sup>7</sup> The predicted figures in these two sets of tables are much alike, but in this study we are reporting only on the figures from Ungerleider and Clark. We also measured the cardiothoracic ratio.

In his recent report Hodges<sup>8</sup> makes it clear that there is no accurate way to measure precisely the size of the heart, nor within narrow limits to determine the presence of enlargement, but if broader limits are allowed a reasonable degree of certainty of enlargement can be attained. It has for years been recognized that the cardiothoracic ratio is not a reliable index of enlargement (Kurtz). If the usual figure of 50 per cent is taken as the criterion of enlargement, one will miss many hearts that are definitely enlarged, but if a heart attains this rather considerable transverse diameter there is hardly any doubt that it is enlarged, unless the heart is clearly lying transversely above a definitely high diaphragm. For this reason we adopted this figure as one of our criteria of enlargement. In order to detect those enlarged hearts which had not yet attained a cardiothoracic ratio of 50 per cent we used the prediction tables of Ungerleider and Clark.<sup>9</sup>

7. Kurtz, C. M.: *Orthodiascopy*, New York, The Macmillan Company, 1937.

8. Hodges, F. J.: Determination of Heart Size, *Am. J. Roentgenol.* **42**:1 (July) 1939.

9. Ungerleider, H. E., and Clark, C. P.: A Study of the Transverse Diameter of the Heart Silhouette with Prediction Table Based on Teleroentgenogram, *Proc. A. Life Insur. M. Dir. America* (1938) **25**:84, 1939.



We did not consider a heart enlarged unless the transverse diameter was 10 per cent greater than the predicted value.<sup>10</sup> A study of 137 normal controls showed this to be a satisfactory standard.

#### RESULTS

There were 148 patients among the 317 studied who had definite arteriovenous nicking (table 2), and 142 (or 96 per cent) of the 148 had enlargement of the heart (a cardiothoracic ratio of 50 per cent or above or a heart diameter 10 per cent above the predicted transverse value). We are unable to learn why the other 6 patients did not have enlargement of the heart. In looking over the teleroentgenograms of this group we did not find a single one in which any good clinician would not have considered the heart enlarged, even without the formality of measurement. We may say, then, with only slight possibility of error, that definite arteriovenous nicking will be accompanied by enlargement of the heart; this is true even if the blood pressure is normal at the time of the examination, which it often is. We may also say that if the patient has definite arteriovenous nicking and enlargement of the heart is found, the enlargement is primarily due to hypertension.

We may properly speculate, if enlargement of the heart is almost always found in the presence of arteriovenous nicking, which comes first. In order to throw some light on this, we studied the incidence of enlargement of the heart (using the aforementioned criteria) in 74 hypertensive patients without arteriovenous nicking. Of these, 23 (31 per cent) had enlarged hearts (table 3). This would seem to be a rather high incidence of enlargement of the heart to be compatible with the idea that the two conditions appear about the same time.

It is apparent that in most cases enlargement of the heart takes place before arteriovenous nicking, though we had 6 patients (out of 148) for whom the reverse was true. If patients with severe coronary arterial (proved clinically and electrocardiographically) syphilitic or rheumatic lesions of the heart are excluded from the group of hypertensive patients

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10. Orthodiascopy was not employed, as we thought this method had little or no advantage over the teleroentgenographic and is subject to many more errors in technic. The great error in measuring the heart size is due to the fact that one is unable to measure the volume of the heart during life. Unhappily, late antemortem and early postmortem changes prevent one from determining accurate heart size even at necropsy. Orthodiascopy, as well as teleroentgenography, is subject to this great error; so the possible advantages of this method, even in the hands of the keenest technicians, are slight indeed. During the course of this study we wrote to the cardiologists in fourteen of the leading medical schools of the United States. Of the twelve that gave answers, seven still use cardiothoracic ratios, four use orthodiascopy and five use teleroentgenograms with prediction tables to determine the expected transverse diameters. Those using cardiothoracic ratios indicated that they did so out of indifference to the problem of early changes in heart size. This seems a deplorable state, as all recent studies have shown the fallibility of this method.

without arteriovenous nicking, enlargement of the heart is found in only 5 cases (6.7 per cent). However, there is no point in trying to exclude patients with coronary heart disease from a group of those with hypertension. The two diseases are constant partners in the destruction of man. But this knowledge forces one to be on guard for other lesions when an enlarged heart is discovered in a hypertensive patient and search of the retinal arteries fails to reveal arteriovenous nicking.

This knowledge has been of great clinical value to us in relation to all forms of heart disease, for hypertension occurs frequently with other diseases of the heart, such as chronic coronary arterial, syphilitic or rheumatic heart disease, and it is valuable to have some method of

TABLE 2.—*Incidence of Arteriovenous Nicking With and Without Associated Enlargement of the Heart\**

	Number of Patients	Percentage
Nicking present, heart enlarged.....	142	95.7
Nicking present, heart normal in size.....	6	4.3

\* The criterion of enlargement was a cardiothoracic ratio of 50 per cent or above or a heart diameter 10 per cent above the size predicted according to the tables of Hodges and Eyster.

TABLE 3.—*Relation of Absence of Arteriovenous Nicking to Enlargement of the Heart\**

	Number of Patients	Percentage
Nicking absent, heart enlarged.....	23	31
Nicking absent, heart normal in size.....	51	69

\* The criterion of enlargement was a cardiothoracic ratio of 50 per cent or above or a heart diameter 10 per cent above the size predicted according to the tables of Hodges and Eyster.

recognizing the importance of the factor of hypertension. This has become so important to us that we begin all cardiac examinations by a retinal study.

We have applied these same statistical analyses to the other two groups of patients, those with early arteriovenous nicking and those with moderate arteriovenous nicking (table 4). It is obvious that early arteriovenous nicking has no relation to the size of the heart, since less than half (41 per cent) of these patients had enlargement of the heart. However, moderate arteriovenous nicking is almost as valuable an index as definite arteriovenous nicking, since 86.3 per cent of this group had enlarged hearts. As a matter of interest we have combined these figures in table 5, in order to show the distribution of the retinal arterial changes in the patients with enlarged hearts and the distribution of such retinal

changes in patients with hearts of normal size. It is worth while to point out that among the patients with enlarged hearts arteriovenous nicking was absent or in an early state in only 19 per cent, whereas definite or moderate nicking occurred in 81 per cent. Now, in the group with hearts of normal size (table 6), 88 per cent had either normal crossings or only an early degree of arteriovenous nicking, whereas in only 12 per cent was the nicking moderate or definite. If all patients with serious coronary arterial disease were eliminated these totals would of course be much more striking.

TABLE 4.—*Incidence of Early and Moderate Degrees of Arteriovenous Nicking With and Without Associated Enlargement of the Heart*

	Number of Patients	Percentage
Early arteriovenous nicking.....	43	
Heart enlarged .....	18	41.9
Heart normal in size.....	25	58.1
Moderate arteriovenous nicking.....	51	
Heart enlarged .....	44	86.3
Heart normal in size.....	7	13.7

TABLE 5.—*Incidence of Arteriovenous Nicking in Two Hundred and Thirty-Three Patients with Enlarged Hearts and Eighty-Three Patients with Hearts of Normal Size*

	Degree of Nicking	Number of Patients	Percentage
Heart enlarged .....		233	
	None	26	11.2
	Early	18	7.7
	Moderate	44	18.9
	Definite	145	62.2
Heart normal in size.....		83	
	None	48	57.8
	Early	25	30.1
	Moderate	7	8.5
	Definite	3	3.6

#### RELATION OF ARTERIOVENOUS NICKING TO RENAL FAILURE

It is impractical to measure renal function accurately for clinic patients, so we were unable to determine precisely the relation between degrees of retinal arterial change and the amount of renal damage present, but we can say positively that in every instance in our series arteriovenous nicking occurred before permanent renal failure in patients with benign essential hypertension. Therefore, if one encounters a patient with permanent renal failure in whom arteriovenous nicking is absent one can be reasonably sure that he is suffering from some other form of nephritis than that due to late benign essential hypertension. Renal failure may occur too quickly in a case of malignant hypertension

to allow development of arteriovenous nicking. We may say, then, that arteriovenous nicking is a useful sign in the differential diagnosis of chronic nephritis associated with late stages of benign essential hypertension and chronic glomerulonephritis, malignant hypertension or other forms of renal disease.

#### SUMMARY AND CONCLUSIONS

We were able to show by this study of 317 patients with hypertension that retinal arteriovenous nicking is so closely related to enlargement of the heart that if this lesion is found we may expect to find an enlarged heart. Furthermore, if this lesion is found in a patient with enlargement of the heart, the latter condition can be accounted for by hypertension, even if the blood pressure is normal at the time of examination. We may also state that if the heart of a hypertensive patient is enlarged and no arteriovenous nicking is found, the enlargement is not likely to be due to hypertension alone and a careful search for other lesions, such as those of severe coronary arterial disease, syphilis or rheumatic fever, is clearly indicated.

There is apparently no relation between the early change in the retinal arteries, which we have designated early arteriovenous nicking, and enlargement of the heart, but the later change, which we have called moderate arteriovenous nicking, is definitely related to enlargement of the heart, though not so closely as the fully developed lesion (definite arteriovenous nicking).

Arteriovenous nicking is important in the differentiation of the chronic nephritis associated with late hypertension and chronic glomerulonephritis.

It is hoped that this study will help to show the importance of careful observation of the changes in the retinal vessels and the necessity for more accurate description. We see too many reports, even from the best institutions, in which retinal arteriosclerosis is evaluated as 4 plus or grade 3 but the lesions are not described. Such a notation is meaningless. It is much more valuable to state whether arteriovenous nicking, extremely narrow arteries, changes in the caliber in arteries, etc., are present.

# FIBER DISSOCIATION IN PERIPHERAL NEUROPATHY

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The various functions of the peripheral nerve are not uniformly affected in the peripheral neuropathy accompanying alcoholism and other conditions leading to disturbed nutrition. With regard to sensation, it has been observed that modalities which are eventually to be carried in the posterior columns, and which are newer in the developmental (phylogenetic) scale, are likely to be impaired earlier and more severely. Neurologic textbooks<sup>1</sup> note that light touch, position and vibration senses are relatively severely affected, while pain sense may be either fairly well preserved or, more commonly, preserved in a "paradoxic" form.

In this paper we have attempted to correlate these observations with certain experimental, clinical and metabolic data.

## FIBER TYPES

The most extensive attempt to group fibers in the peripheral nerves on a functional basis was that of Head,<sup>2</sup> who divided sensation into the following types:

1. Epicritic sensation: This includes light touch sensation over hairless parts, cutaneous localization, two point discrimination, discrimination of size and discrimination of temperatures between 26 and 38 C.

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Read at the meeting of the New York Academy of Medicine, Section of Neurology and Psychiatry, April 9, 1941.

From the Neuropsychiatric Division of the Third (New York University) Division of Welfare Hospital; the Medical Service of the Psychiatric Division, Bellevue Hospital, and the Departments of Psychiatry and Medicine, New York University College of Medicine

1. (a) Gowers, W. R.: A Manual of Diseases of the Nervous System. Philadelphia, P. Blakiston, Son & Co., 1888. (b) Grinker, R. R.: Neurology, ed. 2, Springfield, Ill., Charles C. Thomas, Publisher, 1937. (c) Wechsler, I. S.: A Textbook of Clinical Neurology, ed. 2, Philadelphia, W. B. Saunders Company, 1932. (d) Brain, R.: Diseases of the Nervous System, New York, Oxford University Press, 1933.

2. Head, H.: Studies in Neurology, New York, Oxford University Press, 1920, vol. 2.

2. Protopathic sensation: This includes cutaneous pain, pain due to physical factors or to hair plucking and discrimination of temperature in extreme ranges.

3. Deep sensation: This includes recognition of pressure, pain due to excessive pressure, recognition of muscle movement, localization of application of pressure and recognition of joint motion due to passive movement.

Head expressed the belief that in the cord itself a regrouping of these three main streams occurs. All impulses for pain (both deep and superficial) and for temperature discrimination (both epicritic and protopathic) travel together. Touch impulses, however, may traverse more than one path in the cord. Head stated the belief that the spinal cord is the site of most of the transmutation to the secondary level of sensation. This involves a regrouping of impulses into specific sensory groups, as well as separation of afferent sensory and nonsensory (coordinating) impulses.

Head had no evidence available, however, to show that functional differentiation in the peripheral nerve could be correlated with anatomic variations in fibers or with the speed of transmission of impulses, but this gap in knowledge has been filled by Gasser and his associates.<sup>3</sup>

The latter authors recorded the grouping of fibers in the isolated sensory nerve by studying the action potential waves obtained by direct electrical stimulation at various strengths. As the strength of the stimulus was increased, three distinct groups of waves were obtained, the first with relatively light shocks, the second when the stimulus was increased to ten times the original threshold and the third only after the stimulus reached a level one hundred times the original threshold, and then only after a perceptible delay. The waves were labeled the A, B and C waves, respectively, and the fibers transmitting each were similarly designated. The authors, using the saphenous nerve of the cat, then measured the speed at which these waves travel. The A waves are transmitted at a speed of 30 to 75 meters per second, the B waves at the rate of 15 to 25 meters per second and the C waves at the relatively slow rate of 1 to 2 meters per second, which accounts for the delay in their appearance.<sup>4</sup>

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3. (a) Gasser, H. S.: Conduction in Nerves, in Relation to Fiber Types, *A. Research Nerv. & Ment. Dis., Proc.* **15**:35, 1935. (b) Clark, D.; Hughes, J., and Gasser, H. S.: Afferent Function in the Group of Nerve Fibers of the Slowest Conduction Velocity, *Am. J. Physiol.* **114**:69, 1935.

4. The terminology here presented is that given by Gasser, in 1935, and we have continued to use it throughout this paper for purposes of simplicity. Subsequently, however, Erlanger and Gasser (*Electrical Signs of Nervous Activity*, Philadelphia, University of Pennsylvania Press, 1937) preferred to consider the B elevation

It has been previously noted that within a group the speed of the impulse is proportional to the diameter of the fiber. This is not strictly true for fibers of different structural and electrophysiologic qualities, but it is important for our purposes that the C waves have been found to be transmitted by the unmyelinated fibers of very small diameter.<sup>5</sup> The A waves travel in a group of large myelinated fibers and the B waves in a group of smaller myelinated fibers with slightly different qualities.

Several attempts have been made to determine the function of fiber groups and to correlate fiber size with sensory modalities. Heinbecker, Bishop and O'Leary<sup>6</sup> stimulated electrically the proximal end of an exposed nerve in a human amputation stump. The largest and most irritable fibers were found to transmit touch impulses, but a slightly stronger stimulus, still insufficient to produce C waves, produced pain. This indicates clearly that certain pain impulses are carried in fibers other than C fibers.

Clark, Hughes and Gasser<sup>3b</sup> showed by progressive increases in electrical stimulation of the saphenous nerve of the anesthetized cat that at the exact point at which the stimulus became sufficiently strong to cause the appearance of C waves marked augmentation of the respiratory and circulatory reflexes occurred. This indicated to the investigators that the C fibers (1) carried afferent impulses and (2) transmitted pain.

Furthermore, cocaine block of the peripheral nerve (in the dog) was found to cause initial disappearance of the C waves, followed later by falling out of the A and B waves, an indication that cocaine blocks the smallest fibers first and the largest last. In man the order in which the various sensory modalities disappear is that of cold, warmth, pain and pressure.<sup>3a</sup> Assuming that in man the largest fibers are similarly most resistant to cocaine, it may be inferred that in the sensory nerve the largest fibers carry sensations of pressure, since these are affected last. The largest fibers which carry sensations of pain must be somewhat smaller than these.

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of the electroneurogram of the saphenous nerve as a subdivision ( $\delta$ ) of the A fibers. They confined the B elevation to the activity which appears in the fastest fibers in the gray rami and which does not occur in the sensory nerve. The A and C fibers mediate both sensory and motor activity (Grundfest, H.: *Bioelectric Potentials*, in Luck, J. M., and Hall, V. E.: *Annual Review of Physiology*, Stanford University, Calif., Stanford University Press, 1940, vol. 2, p. 213). In the latter classification, the B fibers are known to occur only in the preganglionic nerves of the autonomic system and probably also in the postganglionic fibers of the ciliary nerve (Grundfest, H.: *Properties of Mammalian B Fibers*, *Am. J. Physiol.* **127**:252, 1939). An excellent experimental survey of this entire problem has recently been made by Zotterman (*Touch, Pain and Tickling*, *J. Physiol.* **95**:1, 1939).

5. Ranson, S. W., cited by Gasser.<sup>3a</sup>

6. Heinbecker, P.; Bishop, G. H., and O'Leary, J.: *Pain and Touch Fibers in Peripheral Nerves*, *Arch. Neurol. & Psychiat.* **29**:771 (April) 1933.

On the other hand, when isolated cat nerve is rendered ischemic by a pneumatic cuff,<sup>3a</sup> the larger A and B fibers are the first to be completely blocked. At this point, a "considerable fraction of the C fibers are still found to be functioning; and stimulation of these produces reflex effects." The same result is obtained whether the sphygmomanometer cuff is applied to the whole limb or whether pressure is applied directly to the nerve trunk, the effect being interpreted as the result of local ischemia of the nerve trunk itself.<sup>7</sup>

#### THE DOUBLE PAIN RESPONSE

The experiments just described indicate that pain sensation is carried both by fast and by slow fibers. This requires some explanation. It has been recognized for some time<sup>8</sup> that a single pinprick of moderate intensity applied to the skin of the arm or leg results in two sensations. The first can be detected almost immediately after the stimulus as a localized, distinct, not unpleasant prick. The second is more diffuse, and if the stimulus is at all intense, the sensation is unpleasant and somewhat prolonged.

Lewis and Pochin<sup>8</sup> by the use of cocaine were able to eliminate the second response while the first was still perceptible, and by asphyxia to eliminate the first response while the second was still preserved. They measured the time necessary for the second response to be perceived and found the delay to be 2.0 seconds from the toe, 1.1 seconds from the knee and 0.8 seconds from the thigh. The difference was evidently a reflection of the time necessary for transmission of the impulse along the nerve fibers at a relatively slow rate and was in proportion to the distance traveled.

They concluded, therefore, that the sensation of pain is transmitted by two sets of fibers, a fast group (A and B) and a slow group (C). The velocity of transmission along fibers of the C group (1 to 2 meters per second) accounts satisfactorily for the delay and would allow its prediction.

This work confirms the electrophysiologic observation that pain sense is carried by two distinct groups of fibers. In asphyxia of the sensory nerves, the same investigators<sup>8</sup> found that the defects in the senses of touch, cold, warmth and fast conducted pain begin almost simultaneously, while the defect in slowly conducted pain sense comes later and is preceded by an exaggerated pain response. Most of the sensory modalities decline slowly but are eliminated completely within a relatively short

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7. Lewis, T., and Pochin, E. E.: The Effects of Asphyxia and Pressure on the Sensory Nerves of Man, *Clin. Sc.* **3**:141, 1938. Clark, Hughes and Gasser.<sup>3b</sup>

8. Lewis, T., and Pochin, E. E.: The Double Pain Response of the Human Skin to a Single Stimulus, *Clin. Sc.* **3**:67, 1937.



period of each other. Touch sense, however, may be lost early. In general, no precise relation between the falling out of specific modalities and the fiber conduction rate can be demonstrated except the constant preservation of the sense of slowly conducted pain (C fibers) well beyond the time of falling out of sensations of touch, vibration, joint position and rapidly conducted pain (A and B fibers). In short, pain sense persists after other sensations have been lost. Just before the onset of complete analgesia this second pain response becomes most intense and conspicuously long lasting.

Local chilling of a peripheral nerve trunk causes the dropping out of functions in an order somewhat different from that observed with asphyxia. Here too, however, delayed pain sense is retained after most other modalities have been lost, and again marked hyperalgesia occurs.<sup>9</sup>

These observations are also confirmed by the results of the *in vitro* studies of Gerard.<sup>10</sup> He observed that when nerves are subjected to anoxia in a closed chamber fibers are not blocked in a homogeneous or continuous fashion but fall out in groups, in an order probably determined by fiber diameter. In this type of experiment the block occurs first in groups which have a higher rate of metabolism. Replacement of the fluid in which the fibers are bathed has no effect in preventing or delaying block. This indicates that block is due to exhaustion of an oxidizing reserve and militates against the supposition that it is due to the accumulation of metabolites. This principle is of considerable importance in the interpretation of *in vivo* asphyxia experiments. In conjunction with Bickford's work (production of hyperalgesia without the factor of impeded blood flow), it offers an explanation of the sensory phenomena independent of humoral mechanisms.

#### PLANTAR DYSESTHESIA

Plantar dysesthesia is a term which we have applied to an abnormal sensitivity of the sole of the foot to scraping. It has been variously called "hyperalgesia,"<sup>2</sup> "paradoxic pain"<sup>1d</sup> and "plantar hyperesthesia."<sup>11</sup> This phenomenon is common in cases of partial damage to the peripheral nerves<sup>2</sup> and of the peripheral neuropathy accompanying alcoholism.<sup>12</sup> Beyond noting its presence, clinicians have been little concerned with its physiologic importance.

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9. Bickford, R. G.: The Fiber Dissociation Produced by Cooling Human Nerves, *Clin. Sc.* **4**: 159, 1939.

10. Gerard, R. W.: Response of Nerve to Oxygen Lack, *Am. J. Physiol.* **92**: 498, 1930.

11. Jolliffe, N.: Diagnosis, Treatment and Prevention of Vitamin B<sub>1</sub> Deficiency, *Bull. New York Acad. Med.* **15**:469, 1939.

12. Brain.<sup>1d</sup> Jolliffe.<sup>11</sup>

Head suggested that this type of sensation, although exaggerated, need not be irritative in origin but might well be the expression of an actual deficiency of function. He implied that certain afferent (epicritic) impulses may exert an inhibitory effect on other (protopathic) impulses.

The condition known as protopathic sensibility arising from lesions of the peripheral nerves is characterized by an overresponse to painful and to thermal cutaneous stimuli. This overresponse is due to the uncontrolled action, on normal sensory centers, of impulses capable of exciting sensations heavily charged with feeling-tone.<sup>2</sup>

Rivers and Head<sup>2</sup> pertinently suggested that the cornea (inadequately supplied with touch fibers) is exquisitely sensitive. Lewis and Pochin<sup>13</sup> (in asphyxia) also noted exaggeration of the second pain response, with the progressive loss of other sensory modalities.

A possible *modus operandi* has been suggested by Gasser<sup>14</sup>: "It is quite possible that the function of impulses which run on ahead of the others is to adjust the excitability of the synapse in preparation for the arrival of later impulses."

One may speculate that normally most of the blow is cushioned by the previous preparation of the synapse by early arriving impulses. When the fast fibers are blocked, the force of the impulses transmitted by the slow fibers is allowed to pass undamped, and the result is a rush of unpleasant feelings, which may occur after an apparent delay in perception. It seems plausible, therefore, to account for the hyperalgesia, or dysesthesia, which occurs in the course of asphyxial block by interpreting it as the result of impulses which have traveled along slowly conducting fibers, reaching synapses not properly inhibited by rapidly traveling impulses. The uninhibited impulse is thus perceived at an intensity much greater than normal.

Furthermore, this phenomenon is not confined to lesions of the peripheral nerves. Dysesthesia has classically been associated with lesions in the region of the thalamus. In cases of such lesions, Head<sup>2</sup> described the response to pinprick as slow and persisting long after stimulation had ceased. His patients described the sensation experienced when the tips of the fingers were drawn over the affected sole as follows: "It's burning, as if you were tearing the skin off" and "like nails digging into the flesh." These responses bear a striking similarity to those elicited from persons with the peripheral neuropathy accompanying alcoholism or from patients in whom dysesthesia has been produced by asphyxia of a limb (see "Experimental Study"). In addition, the threshold for simple pinprick is high in all three conditions. Head

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13. Lewis and Pochin (footnotes 7 and 8).

14. Gasser, H. S.: Control of Excitation in the Nervous System, in Harvey Lectures, 1936-1937, Baltimore, Williams & Wilkins Company, 1937, p. 169.

mentioned that even the vibrating tuning fork may cause an unpleasant sensation in patients with the "thalamic syndrome." This, too, is a not infrequent observation in cases of the peripheral neuropathy of alcoholism. In general, Head asserted,<sup>2</sup> "a stronger prick and greater pressure are required to cause pain on the affected side, but when once evoked, the pain was much less bearable and produced a stronger reaction." In many cases the patient's reactions were delayed and explosive. The actual time, however, was not measured.

Head<sup>2</sup> expressed the belief that this state occurred as the result of interruption of impulses normally traveling from cortex to thalamus.

The only function which can be ascribed to these corticothalamic paths is that through them the cerebral cortex controls, in some way, the activity of the thalamus. If this view is correct, lesions which interrupt these paths, but leave intact the main substance of the optic thalamus, must lead to a permanent over-activity of functions exercised by that organ.

This inhibitory mechanism is similar to that postulated for the peripheral nerve. We wish, furthermore, to emphasize the clinical similarity.

Less well known is the occurrence of a comparable phenomenon with lesions elsewhere in the central nervous system. Kendall<sup>15</sup> has reported 3 cases of disease of the brain stem in which delayed dysesthesia was present. The delay was of the same order as that observed with lesions of the peripheral nerves, namely, about 2 seconds. He postulated that the central nervous system must contain some system of fast and slow fibers similar to that described by Gasser for the peripheral nerves, with a corresponding inhibitory mechanism and timing arrangement.

#### SENSORY DISSOCIATION IN PERIPHERAL NEUROPATHY

Jolliffe<sup>11</sup> has described the order of development of sensory and motor defects in the peripheral neuropathy accompanying alcoholism as follows:

Heaviness of the lower extremities, and calf muscle cramps are usually the first symptoms. These are followed by paresthesias in the toes and fingers, burning of the feet, and pain in the legs. It should be emphasized that pain, though nearly always present, can often be elicited only by a leading question. Calf muscle tenderness and plantar hyperesthesia are as a rule the earliest objective signs. The hyperesthesia may extend up the ankles and legs in a sock distribution. Vibratory sensation may be lost in the toes. These signs we classify as suggestive, and a positive diagnosis of polyneuritis is not made, as circulatory disturbances may cause these or very similar findings. When, however, in addition to these signs, the ankle jerks are absent, a diagnosis of mild polyneuritis can be made. As the deficiency continues, the sensory and motor changes advance, the knee jerks disappear, position sense in the toes becomes impaired, atrophy of the calf muscles develops and foot drop follows.

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15. Kendall, D.: Some Observations on Central Pain, *Brain* 62:253, 1939.

Furthermore, plantar dysesthesia was a constant finding in 32 cases of acute neuropathy accompanying alcoholism,<sup>16</sup> but dysesthesia of the delayed type does not seem to have been studied as such in these cases.

#### SUMMARY OF LITERATURE

A review of the literature to date, therefore, reveals the following essential points:

1. There is good evidence that the sensory peripheral nerve carries three different types of fibers. These vary in size, in irritability and in speed of impulses. The smallest, denoted by Gasser as C fibers, are nonmedullated, are least irritable, are smallest in diameter and transmit impulses at a speed far lower than that of the others. The faster conducting fibers, which are medullated, are known as the A and B fibers.

2. With regard to the functions of the various types of fibers, Gasser<sup>14</sup> concluded:

The fastest fibers carry touch impulses but not pain, and the C fibers carry pain, without touch or pressure. However, pain is also found in the second elevation (B) and overlaps warmth and probably pressure. . . . There must be some other reason than the modalities of sensation for the numerous velocities.

3. When fibers are blocked by asphyxia, the C fibers continue to function for some time after the A and B groups have been completely blocked.

4. In contrast, when the fibers are subjected to the action of a local anesthetic, such as cocaine, the C fibers are the first to be blocked.

5. The sensation carried by the C fibers has been identified with delayed pain.

6. The presence of double pain sensation has been demonstrated under normal conditions. The delay in perceiving "second pain" has been shown to be of the order of magnitude which would be expected if the sensation were transmitted by the C fibers.

7. When asphyxia results in the loss of sensations carried in the larger fibers "second pain" is not only preserved but becomes distorted and unpleasant. The threshold for pain perception, however, becomes high.

8. The phenomenon of delayed plantar dysesthesia appears to be the result of the continuing transmission of impulses along the C fibers, while all the faster (A and B) fibers have been blocked. It seems

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16. Goodhart, R., and Jolliffe, N.: Effects of Vitamin (B<sub>1</sub>) Therapy on the Polyneuritis of Alcohol Addicts, *J. A. M. A.* **110**:414 (Feb. 5) 1938. Jolliffe, N.; Colbert, C. N., and Joffe, P. M.: Observations on the Etiologic Relationship of Vitamin B (B<sub>1</sub>) to Polyneuritis in the Alcohol Addict, *Am. J. M. Sc.* **191**:515, 1936.

possible that the fast (A and B) fibers raise the threshold of the sensory synapse in the dorsal gray matter for the reception of later and slower impulses (C fibers). With asphyxiation and the falling out of the fast (A and B) fibers, this normal preparation of the synapse does not occur. At this point sensation is perceived in an exaggerated and abnormal fashion.

#### EXPERIMENTAL STUDY

The loss of function in a limb which is subjected to acute anoxia was studied in 10 subjects free of disease affecting the peripheral nerves. We employed the technic previously described by Clark, Hughes and Gasser<sup>3b</sup> and Lewis and Pochin,<sup>7</sup> using the leg rather than the arm. The blood supply to the leg was interrupted by means of a blood pressure cuff applied above the knee and inflated to a pressure well above the systolic (190 to 210 mm. of mercury).

We followed the progress of defects in light touch and superficial pain sense, vibratory sensation in the toes, toe position sense, the achilles tendon reflex, strength of dorsiflexion of the toes, plantar sensation (scraping) and reaction time for the plantar sensation. In a number of cases the cold and warmth sensations were also tested.

The nature of the experiment required frequent testing. The number of functions tested for was therefore limited, and the time intervals between tests were kept at five to seven minutes to avoid excessive fatigue. For the same reason, relatively gross methods of testing (such as those employed in clinical examinations) were used. We believe our observations are experimentally valid because we always had the other, normal leg for comparison. This made it possible to detect defects much earlier than would otherwise have been possible.

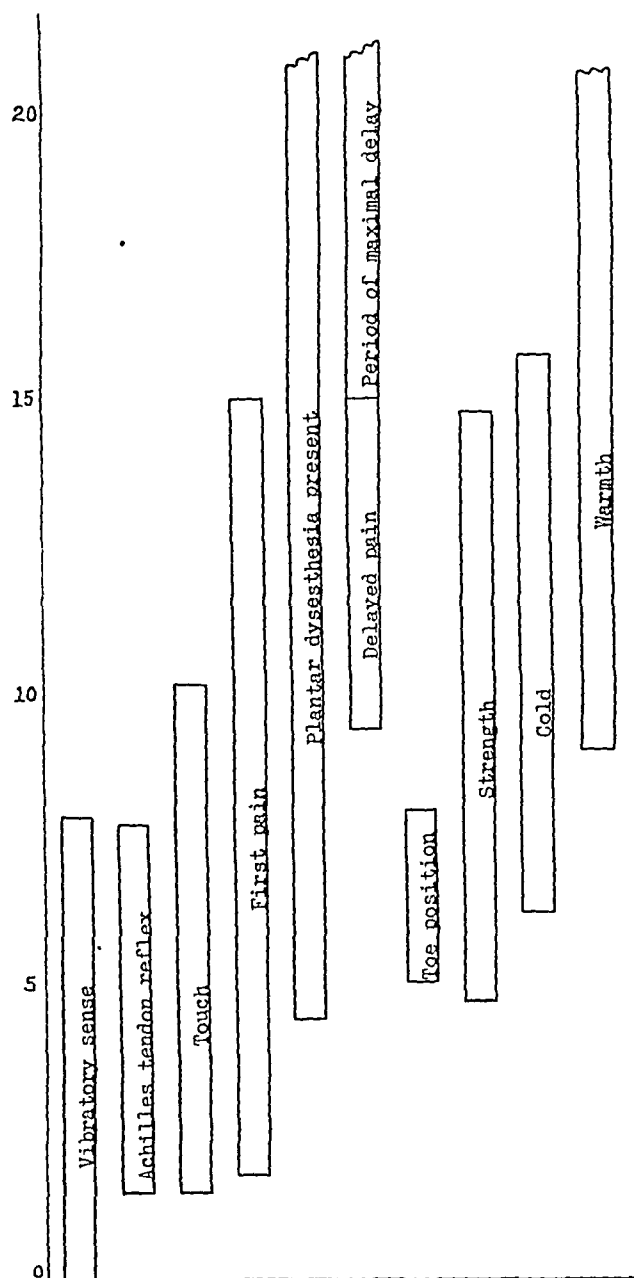
The results, in general, agree with those of the aforementioned experimenters. The accompanying graph indicates the appearance of sensory defects in the 10 subjects studied by this method. While there was a good deal of variation from case to case in the precise time of appearance of individual defects, several features which we believe to be of significance were common to all.

1. Touch and vibratory senses were always affected early, as compared with pain or position sense. Depression of the ankle jerk followed closely on the impairment of touch and vibratory sense.

2. Superficial pain sense was affected shortly after the earliest defects appeared, but was practically never lost first.

3. Position sense, while affected late, nevertheless was one of the functions complete loss of which occurred earliest. Once a defect in position sense could be detected, complete loss was sure to follow within a few minutes. This probably means that early changes in this function cannot be detected by the present clinical methods.

4. Pain sense was never completely lost. After some time the threshold became high and the sensation delayed. We have arbitrarily chosen this point to represent the complete loss of "first pain." We reached this figure by noting the time at which the delay in pain trans-



The loss of function in a foot subjected to interruption of the blood supply. The base line (O) is the point at which the first defect in vibratory sense could be detected. The left border of each bar indicates the first point at which the defect in a given sense could be detected. The right border indicates the first point at which the function was entirely lost. A jagged right border denotes persistence of the function past the point at which the experiment was terminated. The results represent the average values for 9 or 10 patients.

mission reached its maximum. It seems probable that only at this point have all the fast pain fibers been blocked. Furthermore, our figures are in substantial agreement with the observations of Lewis and Pochin.

5. Plantar dysesthesia developed in every case. There is some question in our minds how this sensation (which in every case became delayed) should be classified, but it is undoubtedly closely allied to pain. It was unpleasant in every case but 1 and was usually described as a combination of burning and pain. Typical descriptions of the sensation stated it was "as though my foot was on a hot steam pipe," "like burning and electric shock" and "as though it was cut and was bleeding." When plantar dysesthesia was evident, a pinprick on the dorsum of the foot was felt as delayed, prolonged burning. It was, in any case, a sensation which was never felt in the normal, control foot under similar stimulation.

6. From the time of its appearance, the threshold for producing this sensation was in general rather high. Occasionally, however, a finger drawn along the patient's sole was sufficient to elicit it. Under the latter circumstances, a further period of anoxia required relatively firm scraping with a hard blunt object (such as the handle of a reflex hammer) to produce the sensation.

Delay occurred eventually in every case. When it first appeared, the time necessary for the patient to react to the stimulus was barely more than the reaction time for the opposite, normal side. With prolonged ischemia, further increase was evident, the rate of increase approaching a final limiting value (0.9 to 1.7 seconds).<sup>17</sup>

7. The earliest changes in superficial sensation occurred in each case over the inner and the dorsal surface of the great toe. This area and a few square centimeters behind and laterally were used for repeated testing. In the case of superficial pain, it was necessary to confine testing to localizable pain spots, as some areas of skin seemed to have lost their capacity to transmit pain, while others were still able to do so to some extent.

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17. The measurement of delay was performed as follows: At the beginning of the experiment the patient was required to give a signal as soon as he felt the prick of a pin on the lower part of his foot. The interval between the stimulus and the signal was timed with a stopwatch six or eight times for each foot. The last four or six values, if reasonably close to each other, were averaged to obtain the base reaction time. At intervals throughout the experiment the pinprick reaction time was remeasured for both feet. In every case it was constant on the control side. When the value had reached a maximum on the anoxic side and showed no further increase with successive observations, four to six values were again averaged. The figure thus obtained was considered the average total delayed reaction time. The base reaction time was then subtracted from this to give the final value for delay. This method is admittedly approximate, but since we were interested in the fact that delay occurred and became constant, rather than in its accurate measurement, we deemed the method sufficiently exact for our purposes.

8. The precise observation of defects in the sensations of heat and cold offered some difficulties, and these modalities were completely tested in only 7 patients.<sup>18</sup> The defects in sensation of cold appeared relatively late, and sensation was lost at about the same time that "first pain" had disappeared and delay had become maximal. Perceptible defects in the sensation of warmth appeared extremely late. As a rule, these occurred about the time that touch and vibration senses had completely disappeared. When sensation of pain became delayed, the perception of warmth was generally noted to be similarly delayed in reaching consciousness. The detection of warmth was never completely lost during the period of the experiment, a property which was shared with delayed dysesthesia. This may indicate that pain and warmth impulses travel along similar pathways in the peripheral nerve.

9. At approximately the time of appearance of plantar dysesthesia the power of dorsiflexion of the great toe became impaired. Complete paralysis generally coincided with the appearance of maximal delay in plantar dysesthesia and pain transmission.

10. With the onset of delayed dysesthesia a good deal of local discomfort occurred. The sensation was difficult to describe but was called "tightness" or "a pain" or "just an uncomfortable feeling."

11. The base line used for the chart represents the time at which vibratory sense first became perceptibly impaired. In each case the time was measured from this point. This value was used, rather than the total period of anoxia, because of the tremendous variation in the time (eight and a half to twenty-four minutes) necessary for the first defect to appear. Once this point was reached, the rate of progression of defects varied little among different subjects.

In order to examine further the variation in the length of the anoxic period necessary for defects to appear, we repeated the same experiment on a number of patients with peripheral neuropathy. Despite the pre-existent defects in the peripheral nerve, the further impairment of function took just as long to become manifest as in the average person without peripheral neuropathy.

We may infer, therefore, that the time necessary for the appearance of the first sign of defective sensation is not an index of any fundamental property of the state of the nerve itself, but rather is a reflection of the nutritional reserve supply. These observations are consistent with those of Gerard<sup>10</sup> on the isolated nerve.

12. Vasomotor changes were not observed in detail. After a short period of anoxia vasodilatation was manifested by the mottled cyanosis which is generally associated with clinical occlusion of the vessels of the

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18. The instruments used in stimulation were metal test tubes, 1 cm. in diameter, containing water at a temperature of 10 to 15 or 55 to 65 C.



leg. When the cuff was deflated, there was marked bright pink flushing of the leg, again indicating vasodilatation.

13. The changes were completely reversible. Within 30 seconds of deflation of the cuff, peripheral nerve function had returned almost to normal. It did, however, take 2 to 4 minutes for the complete return of vibratory and light touch sensation. These, it will be recalled, were the first to disappear. In every case, testing at the end of 2 minutes showed some return of the ankle jerk, and at 4 minutes it had returned to normal. There was some discomfort of the "pins and needles" type, which lasted for about 5 minutes. Because of the rapidity of the changes following restoration of the circulation, it was impossible to follow in any greater detail the order of return of function.

#### CLINICAL DATA

In order to illustrate more fully the similarity of the neurologic changes in anoxia to those resulting from the peripheral neuropathy accompanying chronic alcoholism, 2 cases are briefly described.

*CASE 1.—Vascular Occlusion, Femoral Artery.*—C. S., a 68 year old white housewife, entered Bellevue Hospital on Oct. 10, 1940 with hypertensive cardiovascular disease, auricular fibrillation and moderately severe cardiac failure. There was evidence of peripheral arteriosclerosis. No pulse could be felt in either foot, but there was no evidence of frank vascular insufficiency of the extremities.

The next day she complained of pain in the right foot, but it was not until two days later that the lower part of the leg was observed to be cold and cyanotic up to about the knee. A history of previous intermittent claudication was elicited at this time. On October 17 examination revealed signs typical of arterial occlusion of the right leg. The extremity was cold up to the knee and was cyanotic to a point 10 cm. below the knee. The pulse could be detected at the groin but not in the lower portion of the thigh, at the popliteal space or below. Lowering the leg resulted in rapid deepening of the cyanosis and severe pain in less than 2 minutes. Elevation caused blanching within a short period, which disappeared slowly when the leg was lowered to the bed. These changes were not present on the other side, where there were no signs of frank vascular insufficiency.

*Neurologic Examination.*—There was marked plantar dysesthesia of the involved foot, with a high threshold for scraping or superficial pain and a total delay of 2.0 to 2.2 seconds. When the sole was stroked, there was no reaction at all for 2 seconds. Suddenly the patient withdrew her leg, gave facial evidence of severe pain and wept. She described the sensation as unpleasant but was unable to give any further details. A similar phenomenon was evident in testing sensation with pinprick. A light pinprick was not felt at all. A slightly heavier stimulus was felt after 2 seconds as a diffuse, unpleasant burning.

Vibratory and position senses were absent in the toes, and touch sense was absent over the whole foot. The ankle jerk was absent. There was only slight ability to move the toes voluntarily. The calf muscles and the tibia were tender on pressure.

In contrast, the left leg revealed neither dysesthesia nor delayed sensation—pinprick or scraping being perceived within 1 second. There was no defect in sensibility to pinprick or in position sense, although there was slight loss of touch sense and some impairment of vibratory sense. The ankle jerk was absent. These

sensory changes were of the type frequently found in cases of arteriosclerosis of the extremities, without conspicuous circulatory impairment.

On the following day hemiplegia developed, and the patient died a few hours later.

*Autopsy.*—Multiple emboli were present, and the right femoral artery was completely occluded. On the left there was evidence of involvement of the vascular tree but no complete occlusion.

The similarity between these changes and those produced by experimental occlusion is apparent. We have since seen another case of embolization of the femoral artery, with similar sensory changes. In this case, collateral circulation was sufficient to allow complete reversal of the clinical signs and the disappearance of dysesthesia. This case completely confirms our experimental observations and indicates that the syndrome is completely reversible when the vascular supply is promptly reestablished.

*CASE 2.—Severe Peripheral Neuropathy Accompanying Alcoholism, with Vitamin Deficiency.*—H. O., a 42 year old man with chronic alcoholism and a history of prolonged dietary insufficiency, was admitted to the Psychiatric Division of Bellevue Hospital on Sept. 29, 1940, with evidences of moderate intellectual impairment. He was able, however, to cooperate exceedingly well for examination.

There was evidence of severe peripheral neuropathy, with bilateral foot drop, complete areflexia and atrophy and tenderness of the calf muscles.

Of particular note was the presence of severe plantar dysesthesia. The threshold was moderately high for touch and pinprick, but even relatively light stroking of the sole caused an unpleasant burning sensation, which was first observed 2 seconds after the stimulus. Pinprick was also delayed 2 seconds and was burning and unpleasant in character.

Although the sensation of superficial pain was defective only to a moderate degree, that of touch was severely impaired below the middle portion of the skin. Vibratory sense was markedly impaired in the shins and practically completely absent in the ankles and toes. Position sense was absent in the toes but present in the ankles. Sweating and cyanosis of both feet were present.

The upper extremities were similarly but somewhat less severely affected. There were bilateral wrist drop, areflexia and some wasting. When the palms of the hands were scraped with a blunt instrument the patient complained of an unpleasant burning sensation. Impairment of finger position sense, vibratory sense and sense of touch was severe, and that of sense of pain was moderate.

Chemical examination of the blood revealed a high fasting level of pyruvic acid. This metabolic defect has been shown by Bueding and Wortis<sup>19</sup> to be constantly associated with the peripheral neuropathy accompanying alcoholism.

Treatment with large doses of preparations of the vitamin B complex resulted in progressive improvement. After a month, there were some return of position and vibratory sense in the toes, complete absence of tenderness of the calf muscles and marked subsidence of plantar dysesthesia.

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19. Bueding, E., and Wortis, H.: Pyruvic Acid in the Blood and Cerebrospinal Fluid, *Proc. Soc. Exper. Biol. & Med.* **44**:245, 1940. Wortis, H., and Bueding, E.: The Clinical Significance of Pyruvic Acid Content of the Blood and Cerebrospinal Fluid, *Tr. Am. Neurol. A.* **66**:90-94, 1940.

In summary, then, this patient with a severe vitamin B deficiency presented a neurologic picture similar to that in the preceding case, in which the disturbance was purely ischemic in nature, and to that in our cases of experimental ischemia. In the experimental cases, we were able to reverse the process by releasing the cuff. In 1 of our cases of embolism reversal occurred after reestablishment of the circulation. In case 2 reversal was accomplished by correction of the metabolic defect. We wish, furthermore, to stress the fact that this is not uncommon but is the usual picture in cases of the severe peripheral neuropathy accompanying alcoholism.

#### COMMENT

Three types of lesions affecting the peripheral nerve have been described:

In the first type, in which the lesion results from experimentally induced ischemia of a limb, fibers are blocked in groups in a more or less precise and predictable way, although all modalities cannot be sharply separated. Of importance is the fact that the smallest fibers carry "second pain" and that they are the slowest and the most resistant to anoxia. These facts explain the phenomenon of delayed dysesthesia, which occurred in every one of our cases of experimental anoxia.

The second type, in which ischemia occurs as the result of vascular occlusion of a pathologic nature, offers a striking resemblance to the first type. It seems justifiable to infer that the process is fundamentally the same. Here, again, the fibers have been blocked in essentially the same order, and the end result indicates the selective preservation of function in the group of small, slowly conducting C fibers. This is precisely what happened in our experimental subjects.

Finally, the peripheral neuropathy accompanying alcoholism, with nutritional deficiency, resembles the ischemic type in its fundamental features, namely, the early involvement of vibratory sense and loss of reflexes, the rarity of the complete loss of the sense of superficial pain, the almost invariable presence of plantar dysesthesia and the not uncommon phenomenon of delay in pain sensation and in plantar dysesthesia. Here, again, one may infer that the small, slowly conducting C fibers have retained their function after that of the larger and more rapidly conducting A and B fibers has been lost. Delay of 1 to 2 seconds implies almost complete blocking of the A and B fibers—at this point plantar dysesthesia is most marked. Delayed dysesthesia occurs only with severe involvement of the peripheral nerve.

This assumption is further confirmed by the pathologic observations of Greenfield and Carmichael.<sup>20</sup> They studied the peripheral nerves of patients with the peripheral neuropathy of alcoholism and of others with subacute combined sclerosis. They found that in both groups the

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20. Greenfield, J. G., and Carmichael, E. A.: *The Peripheral Nerves in Cases of Subacute Combined Degeneration of the Cord, Brain* 58:483, 1935.

number of large fibers in the peripheral nerves were significantly reduced in ratio and in number as compared with the normal. Swank,<sup>21</sup> studying pigeons which had been deprived of thiamine (vitamin B<sub>1</sub>), so as to produce peripheral neuropathy, found that the large fibers appeared to suffer first and to the greatest extent. As the deficiency grew more marked, the medium-sized fibers were affected, but as a rule the smallest ones remained intact.<sup>22</sup> The resemblance of the changes associated with the peripheral neuropathy of alcoholism to those which result from asphyxia of any variety is an observation of more than purely theoretic interest. The former are now generally recognized as the result of a metabolic deficiency. The similarity between the clinical changes associated with this neuropathy and those encountered in cases of ischemia offers a physiologic explanation for the characteristic sensory dissociation seen in cases of the first-named condition.

#### SUMMARY

The effect of asphyxia on the function of the peripheral nerve has been studied and a characteristic order of loss of sensory modalities demonstrated which is in agreement with the observations of previous investigators.

The significance of the phenomenon of delayed plantar dysesthesia has been discussed, particularly its relation to the persistence of function in the small, slowly conducting, nonmedullated (C) fibers after the large (A and B) fibers have been blocked. We have speculated on the inhibitory function of the rapidly conducting fibers and the application of this mechanism to similar dysesthetic phenomena with lesions elsewhere in the nervous system.

The sensory changes associated with the peripheral neuropathy accompanying alcoholism have been compared with those which occur as the result of experimental or clinical occlusion of the blood supply to an extremity, in terms both of clinical resemblance and of similarities of damage to certain groups of nerve fibers. The significance of the resistance of the nonmedullated (C) fibers to certain metabolic factors (ischemia, avitaminosis) is emphasized.

This work suggests that those portions of the peripheral nerve which conduct impulses at higher rates of speed and which are most irritable have the highest metabolic requirements and are most susceptible to metabolic disturbances. Hence, in cases of avitaminosis or ischemia affecting the peripheral nerve the A and B fibers are most susceptible to damage.

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21. Swank, R. L.: Avian Thiamin Deficiency, *J. Exper. Med.* **71**:683, 1940; personal communication to the authors, 1940.

22. This differs somewhat from the order of block due to asphyxia *in vitro*, in which fibers of medium size causing the second elevation are affected before the large ones. Again, however, small, slowly conducting nonmyelinated (C) fibers remain intact.

# COCCIDIOIDAL ARTHRITIS

REPORT OF A CASE IN WHICH THE ANKLES WERE INVOLVED  
AND THE CONDITION WAS UNAFFECTED BY SULFANIL-  
AMIDE AND ROENTGEN THERAPY

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In 1931 a bulletin was published under the auspices of the California Department of Public Health in which the subject of infection with the fungus *Coccidioides immitis* was reviewed.<sup>1</sup> This bulletin was documented with 172 references and indicated that 286 instances of the disease among human beings had been observed up to that time. By 1938 Dickson and Gifford<sup>2</sup> reported that 495 instances of the disease had been observed in California alone and that the disease had caused 249 deaths. Up to the time of writing (April 1941), 19 additional reports concerning this disease have been listed in the *Quarterly Cumulative Index Medicus*.

Despite this large number of reported cases of coccidioidomycosis and the extensive literature concerning it, only 3 instances of the disease have been recognized at the Mayo Clinic. In the first case, reported by Foley, Love, Broders and Heilman,<sup>3</sup> the patient had coccidioidal osteomyelitis of the skull. In the second case, reported by Craig and Dockerty,<sup>4</sup> the patient had pulmonary and meningeal lesions. In the

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From the Section on Surgical Pathology (Dr. Dockerty) and the Section on Orthopedic Surgery (Dr. Meyerding), the Mayo Clinic.

1. Coccidioidal Granuloma, Special Bulletin 57, State of California Department of Public Health, June 1931.

2. Dickson, E. C., and Gifford, M. A.: *Coccidioides* Infection (*Coccidioidomycosis*): II. The Primary Type of Infection, *Arch. Int. Med.* **62**:853-871 (Nov.) 1938.

3. Foley, M. P.; Love, J. G.; Broders, A. C., and Heilman, F. R.: Coccidioidal granuloma: Report of a Case Originating in Texas, *West. J. Surg.* **48**:738-741 (Dec.) 1940.

4. Craig, W. M., and Dockerty, M. B.: Coccidioidal Granuloma: A Brief Review with Report of a Case of Meningeal Involvement, *Minnesota Med.* **24**: 150-154 (March) 1941.

third case, reported in this paper, the patient had coccidioidomycosis of the ankle joints.

The reason for the extraordinary rarity of coccidioidomycosis in Minnesota lies in the fact that the main reservoir for infection with *C. immitis* is in the distant southern agricultural valley of California, the Sacramento-San Joaquin Valley, particularly its southern reaches, including the two counties of Kern and Tulare. Approximately 90 per cent of reported cases have concerned patients observed in California, and approximately 66 per cent of cases have been reported from the central and southern sections of that state.<sup>1</sup> In California the disease has been reportable since 1928; yet only isolated instances have been observed in other states.

Coccidioidomycosis was discovered in Argentina; the second case was reported from California, by Rixford, and for nearly fifty years California has been a center for research concerning this disease. Tremendous strides in the understanding of the biology of the causative fungus and of the life history of the disease in man have been made by physicians working in that state. With a somewhat doubtful sense of fitness, it has even been suggested that this be known as the "California disease."

#### CLINICAL MANIFESTATIONS OF COCCIDIOIDAL INFECTION

Until recently the fungus *C. immitis* was thought to cause only one type of disease, a serious chronic granulomatous infection with clinical and pathologic features similar to those of tuberculosis. It was known to affect skin, lymph nodes, abdominal and thoracic viscera, meninges, bones and joints. In 1936 Dickson<sup>5</sup> and Smith<sup>6</sup> independently made the notable discovery that the organism may cause not only a serious chronic granulomatous process but an acute, extremely benign disease. Endemic in the Sacramento-San Joaquin Valley area for at least fifty years has been a disease well known to local members of the medical profession and to laymen as "valley fever," "desert fever," "desert rheumatism," "San Joaquin Valley fever" or "the bumps." It is a mild, usually nonfatal illness, characterized by the acute onset of malaise, general aches and pains, "toxic erythema," sore throat with fever and, occasionally, conjunctivitis, and signs of bronchopneumonia appear. Eight to fifteen days after the onset of the disease, at a time when there appears to be general improvement of the patient's condition, lesions typical of erythema nodosum appear, mainly on the shins, occasionally elsewhere on the body.<sup>2</sup>

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5. Dickson, E. C.: "Valley Fever" of the San Joaquin Valley and Fungus *Coccidioides*, California & West. Med. **47**:151-155 (Sept.) 1937.

6. Smith, J., cited by Dickson.<sup>5</sup>

Roentgenologic examination of the thorax at the time of the appearance of erythema nodosum usually discloses the presence of opaque regions which suggest the diagnosis of tuberculosis.

The cause of this disease remained unknown until 1936, when Dickson and Smith found that the fungus *C. immitis* could be obtained from the sputum of a patient who had the disease. Moreover, affected persons react powerfully to the subcutaneous injection of test doses of a broth filtrate ("coccidioidin") from cultures of the organism. For these reasons it is now agreed that valley fever is caused by *C. immitis*.

Many patients are said never to seek medical attention when they have valley fever; others probably receive a diagnosis of "flu" or "pneumonia," especially if erythema nodosum does not appear.

#### MANNER OF INFECTION WITH *C. IMMITIS*

The organism *C. immitis* passes through two phases in its life cycle, one vegetative and one parasitic. The vegetative phase probably takes place in soil or on vegetation. Reproduction in this phase is accomplished by means of chlamydospores, which are minute bodies attached to aerial hyphae of the fungous growth. The parasitic phase occurs in the body of an infected host. The delicate chlamydospores of the vegetative phase may float free in the air and are capable of producing disease in the one who inhales them after an incubation period of one to three weeks. Animals may be so infected experimentally,<sup>7</sup> and there are on record many clearcut instances of infection resulting from inhalation of chlamydospores by human beings, especially laboratory workers who have dealt with the organism grown on artificial solid medium. Valley fever may develop in human beings who inhale the spores. It is rarely followed by coccidioidal granuloma. Only a few cases of proved "inoculation infection" have been reported.<sup>1</sup> One patient was believed to have acquired the infection by pricking the skin with a cactus burr, and infection also has resulted from an abrasion of the skin caused by picking walnuts, by injury with a splinter of wood and so forth. Not all patients suffering from coccidioidal granuloma have given a history of valley fever or inoculation, but this is an aspect of the problem which will require further study.

#### TYPES OF ARTHRITIS ASSOCIATED WITH COCCIDIOIDOMYCOSIS

Involvement of joints occurs both in the acute benign phase and in the more dangerous chronic granulomatous phase of coccidioidal infection. In cases of valley fever, or desert rheumatism, involvement of

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7. Cronkite, A. E., and Lack, A. R.: Primary Pulmonary Coccidioidomycosis: Experimental Infection with *Coccidioides Immitis*, *J. Exper. Med.* **72**: 167-174 (Aug.) 1940.

joints may be distressingly painful but is nevertheless relatively insignificant because the arthritis subsides completely. Involvement of joints in the granulomatous phase of the disease is serious and may be the forerunner of disseminated infection which will lead to death.

*Arthritis of Valley Fever.*—Signs of acute arthritis develop in about a third of patients who have valley fever, usually appearing simultaneously with erythema nodosum.<sup>8</sup> Affected joints are tender to pressure, painful on motion and in some cases are slightly swollen. Effusion into these joints has not been observed, and in no known instance has suppuration taken place. Sometimes conjunctivitis also appears in this stage of valley fever, and often arthritis, conjunctivitis and erythema nodosum appear together, persist about a month and disappear at approximately the same time. Affected joints always clear without residual damage or deformity. Among older people the arthritis is said to be more prolonged than it is among children. No records of roentgenologic examination of such joints are available, to our knowledge.

**Diagnosis:** Valley fever should be suspected particularly among patients complaining of acute arthritis who also present evidence of acute pulmonary infection, whether or not it is accompanied by erythema nodosum. Suspicion should be heightened if the patient has been resident or visiting in southern California. Diagnosis may be established positively by the finding of the organism *C. immitis* in the sputum by direct examination, culture or inoculation of guinea pigs.

**Prognosis:** Notable differences exist between the prognosis for the common acute mild manifestation of coccidioidal infection, or valley fever, and that for the chronic granulomatous phase of the disease. Survival is the rule after the acute type of disease. In only 1 of 354 cases of valley fever known to Dickson and Gifford did the granulomatous phase develop. In this case the patient died. In none of the 432 cases collected by Smith<sup>9</sup> did the granulomatous phase develop. On the other hand, death has resulted in 50 per cent of cases of coccidioidal granuloma. What alteration in the mechanism of immunity or in the virulence of the infecting organism underlies this tremendously important change in prognosis is thus far not known.

**Treatment:** No special methods of therapy have been developed for valley fever. Affected patients are best kept at rest in bed, and measures for symptomatic relief should be employed, including the administration of salicylates, to relieve pain in joints.

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8. Faber, H. K.; Smith, C. E., and Dickson, E. C.: Acute Coccidioidomycosis with Erythema Nodosum in Children, *J. Pediat.* **15**:163-171 (Aug.) 1939.

9. Smith, C. E.: Epidemiology of Acute Coccidioidomycosis with Erythema Nodosum ("San Joaquin" or "Valley Fever"), *Am. J. Pub. Health* **30**:600-611 (June) 1940.



*Arthritis of the Chronic Granulomatous Phase of Coccidioidomycosis.*

—In this stage of the disease, lesions in bones and joints are fairly commonly encountered. Among 256 cases tabulated in the report of the California Department of Public Health in 1931,<sup>1</sup> involvement of joints was noted in 79, as seen in table 1. Often, several joints are involved at one time. Affected joints have in this particular phase of the disease first the appearance of acute, later of chronic, arthritis. Early, the joints are swollen and red; later, fluctuation may appear. Nodular lesions may develop in the skin overlying affected joints. Such lesions may ulcerate and discharge pus containing *C. immitis*. McMaster and Gilfillan<sup>10</sup> expressed the opinion that joints may be primarily affected by direct involvement of the synovial membrane or infection may extend to joints from adjacent foci of coccidioidal osteomyelitis. Of

TABLE 1.—*Involvement of Joints in Seventy-Nine Cases of Acute Granulomatous Coccidioidomycosis*

Joint	No. of Cases
Ankle	33
Knee.	21
Foot	16
Elbow	11
Wrist	10
Shoulder	8
Finger (?)	7
Vertebrae	6
Hip	5
Sternoclavicular	1
Unspecified.	5

24 cases reported by them in which involvement of bones and joints was noted, primary localization in synovial membrane was present in 4 (once in an ankle, once in a hip and twice in a knee joint). In the remaining 20 cases infection of joints had taken place by extension from adjacent areas of bone disease. Progression of the infection is not halted by articular cartilage or epiphysial bone, although intervertebral disks are somewhat more resistant than are vertebral bodies.

**Roentgenographic Manifestations in Joints:** These may mimic the changes seen in cases of tuberculous arthritis. Early lesions are characterized by regions of destruction in articular surfaces, often with evidence of swelling of overlying soft tissues. Cartilage may be destroyed and joint spaces narrowed. There is little tendency toward production of bone in the early lesions of the chronic stage. Later lesions in joints may cause complete disappearance of joint spaces, more

10. McMaster, P. E., and Gilfillan, C. Coccidioidal Osteomyelitis, J. A. M. A. 112:1233-1237 (April 1) 1939.

extensive zones of destruction in articular surfaces and, in some instances, ankylosis.<sup>10</sup> These lesions have been commonly mistaken for those of tuberculous arthritis. Carter<sup>11</sup> pointed out that arthritis both in coccidioidal granuloma and in tuberculosis is predominantly destructive, shows little tendency to heal by production of bone and frequently is accompanied by pulmonary involvement. But whereas tuberculosis appears often to attack joints directly, coccidioidal granuloma usually does so by extension from adjacent bone lesions, and the latter involvement more often affects multiple joints. Taylor<sup>12</sup> found the destructive process in bones, as shown by roentgenograms, to be distinguished by an intensity and rapidity of development not often noted in the presence of tuberculosis.

**Diagnosis:** This condition should be suspected in persons suffering from chronic progressive monoarticular or polyarticular arthritis, particularly if such persons have resided or visited in the region of the San Joaquin Valley. Suspicion should be heightened if serial roentgenograms indicate an unusually rapid progress of the destructive process in bone. As in cases of tuberculosis of bones and joints, an active primary infection may not be demonstrable. The diagnosis must rest on the finding of the organisms in sputum, tissues or pus from a sinus leading from an involved region. Occasionally, the organism has been obtained by means of blood culture.<sup>1</sup>

**Prognosis:** In most recent reports the mortality rate in the chronic granulomatous phase is stated to be at least 50 per cent. The disease kills by becoming generalized. During the terminal phase the patient may display exhaustion and high fever of a septic type, often accompanied by chills, emaciation and marked anemia.

**Treatment:** No therapy has proved to be of specific value for the chronic phase of this disease. Antimony and potassium tartrate, colloidal copper, vaccine, thymol and roentgen therapy have had proponents. Amputation may be a life-saving measure. Hynes<sup>13</sup> recently reported "startling results of sulfanilamide therapy" for 1 patient, but our own therapeutic efforts with this drug were not successful. Dr. Luther Thompson, of the Section on Bacteriology and Parasitology of the Mayo Clinic, has made some preliminary studies of the fungicidal effect of sulfanilamide in vitro, using the particular strain of *C. immitis* which was isolated from our patient. Thus far it would appear that sulfanilamide is not effective against the fungus. In a recent personal com-

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11. Carter, R. A.: Coccidioidal Granuloma: Roentgen Diagnosis, *Am. J. Roentgenol.* **25**:715-738 (June) 1931.

12. Taylor, R. G.: Coccidioidal Granuloma, *Am. J. Roentgenol.* **10**:551-558 (July) 1923.

13. Hynes, K. E.: Coccidioidal Granuloma, *Northwest Med.* **38**:19-21 (Jan.) 1939.

munication, Dr. Charles E. Smith,<sup>14</sup> associate professor of public health and preventive medicine at the Stanford University School of Medicine, San Francisco, stated that there, too, sulfanilamide had been found to be ineffectual in treatment both of the acute and of the chronic phase of the disease in man and also in vitro and in treatment of infection produced experimentally in animals.

#### REPORT OF CASE

The patient, a man aged 25, came to the Mayo Clinic in October 1940, complaining of pain and swelling of both ankles of a year's duration. He had been



Fig. 1.—The condition of the patient's ankles on Oct. 4, 1940. Marked swelling is evident.

born in Arkansas but had lived and worked in the San Joaquin Valley, Calif., for four years previous to the onset of his illness in 1939. He had been employed as foreman of a crew of workers on oil pipe lines. The work frequently was dirty and dusty. His family history was irrelevant, and he had had no previous serious illness.

During May, June and July 1939 he had a dry cough. In July 1939 he thought he had "flu," for he "ached all over" and suffered from headache and his temperature increased to 104 F. His local physician also at first believed this illness represented influenza or grip, but after three days of fever, a generalized

14. Smith, C. E.: Personal communication to the authors.

rash appeared on the patient's face, trunk and extremities. This rash led to the diagnosis of "typhus" by his physician. The rash cleared after three or four days. Fever, during which the temperature was elevated to 102 F., continued for two weeks, and during the second week the patient had "pleurisy" on the right side, with severe pain on respiration. At this point a tuberculin test was made, to which the reaction was negative.

Low grade fever persisted. In August, four months after onset of the cough, a number of red, indurated lesions appeared on the dorsum of either hand and on the outer aspect of the left thigh. These may have represented erythema nodosum, but we could not be certain on the basis of the patient's history. These lesions persisted for two or three weeks, were slightly painful and healed without leaving any scars.

The patient was able to return to work in October 1939 but continued to have low grade fever in the afternoon. Three days after he began to work swelling appeared about the left foot and ankle, with pain on weight bearing. One week later the right foot and ankle swelled and became painful. These swellings persisted, but he continued to work. Diathermy applied to the ankles and "rheumatism" remedies taken by mouth were ineffective.

In September 1940 pain on weight bearing became intolerable and the patient quit work. His condition then remained unchanged until he came to the clinic.

Physical examination of the head, thorax and abdomen at that time failed to reveal anything abnormal. The blood pressure was 130 systolic and 90 diastolic, expressed in millimeters of mercury. Both ankles were swollen, the right more than the left (fig. 1), and on palpation the swellings gave the impression of fluctuation. Pressure over the swollen portions elicited severe tenderness. The lymph nodes overlying Scarpa's triangles were enlarged but not tender.

Laboratory studies, including urinalysis and blood counts, did not reveal any striking abnormalities. There was a slight reduction of the value for hemoglobin, to 12.7 Gm. per hundred cubic centimeters. The result of the flocculation test for syphilis was negative. Results of agglutination tests were negative for *Brucella melitensis*, *Eberthella typhi* and *Proteus X<sub>10</sub>* (Weil-Felix agglutination reaction for typhus fever). Roentgenograms of the thorax were normal, and those of both ankles showed swellings of the soft tissue, with flecks of calcification in the swollen regions. In the left ankle joint (fig. 2) there was marked erosion of the posterosuperior border of the os calcis. Roentgenograms of the ankles in the anteroposterior position (fig. 3) showed marked clouding of the right ankle joint, with possibly some erosion of the joint surfaces.

We recognized that this patient's condition bore a resemblance to tuberculosis, but we were of the opinion that the curious features of the history and the bilateral involvement were atypical of tuberculosis and justified biopsy for final diagnosis.

On October 7 the posteromedial aspect of the right ankle was incised. Part of a sac filled with cheesy necrotic material was removed for biopsy, and culture medium was inoculated with some of the contents. The wound healed by primary intention.

The surgical specimen consisted of mottled brownish yellow tissue having the appearance of granulation tissue. Fresh frozen sections stained with polychrome methylene blue showed a granulomatous lesion with giant cells and epithelioid cells. In addition, many polymorphonuclear leukocytes and monocytes were present,

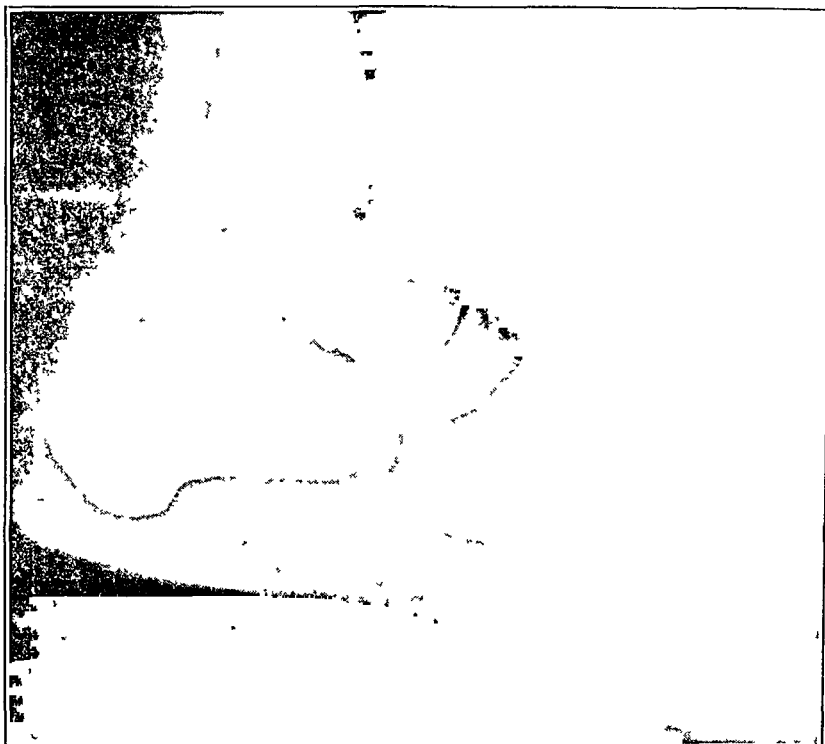


Fig. 2.—A roentgenogram of the patient's left ankle, made on Oct. 2, 1940. Periarticular swelling of the soft tissues and erosion of the posterosuperior border of the os calcis are seen. There is only slight involvement of the ankle joint. Flecks representing calcification may be noted in the soft tissues posterior to the ankle joint.

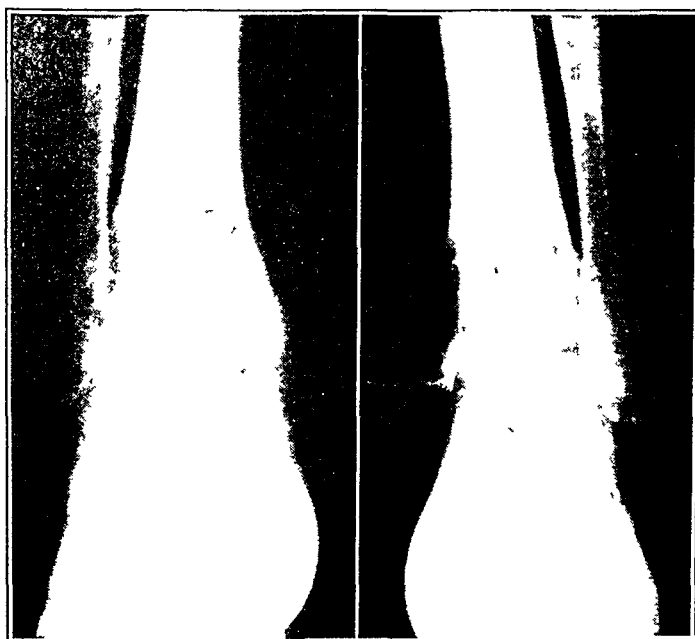


Fig. 3.—An anteroposterior roentgenogram of the ankles, made on Nov. 25, 1940, demonstrating clouding in the shadow of the right ankle joint.

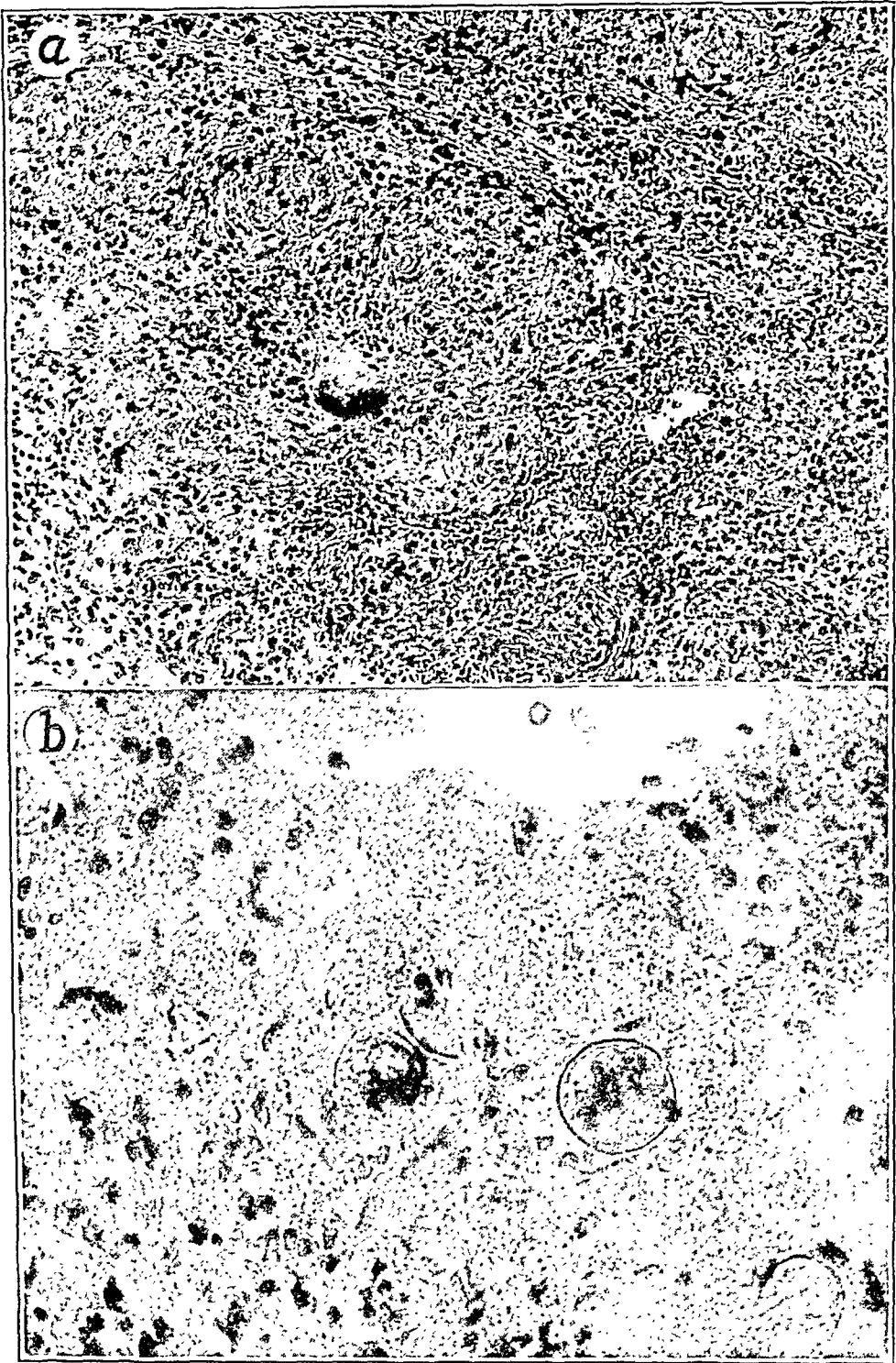


Fig. 4.—(a) Histologic picture similar to that found in the presence of tuberculosis, with "tubercle" formation, large giant cells and foci of acute inflammation. Hematoxylin and eosin;  $\times 150$ . (b) Organisms of coccidioidal granuloma, with double-contoured bodies filled with spores but without budding or mycelial formation. Hematoxylin and eosin;  $\times 450$ .

particularly around focal areas of necrosis, which dotted the microscopic field. Fragments of disintegrating bone in several sections confirmed the roentgenographic evidence of calcium about the joint and suggested that the process was one of destructive osteitis. Occasional "tubercle" formation was observed, which was suggestive of tuberculosis. However, search with high magnification disclosed large, double-contoured, refractile bodies containing minute, rounded, sporelike forms. Some of these double-contoured bodies were seen to be engulfed in giant cells, but others lay free in the intercellular spaces, especially in cellular zones. Budding was not observed, and no mycelial filaments were seen. A diagnosis of coccidioidal granuloma was made on the basis of this examination of fresh tissue.

Of the salient microscopic features in this case, one is shown in figure 4 *A*, in which the resemblance to tissue affected by tuberculosis is striking. Figure 4 *B*

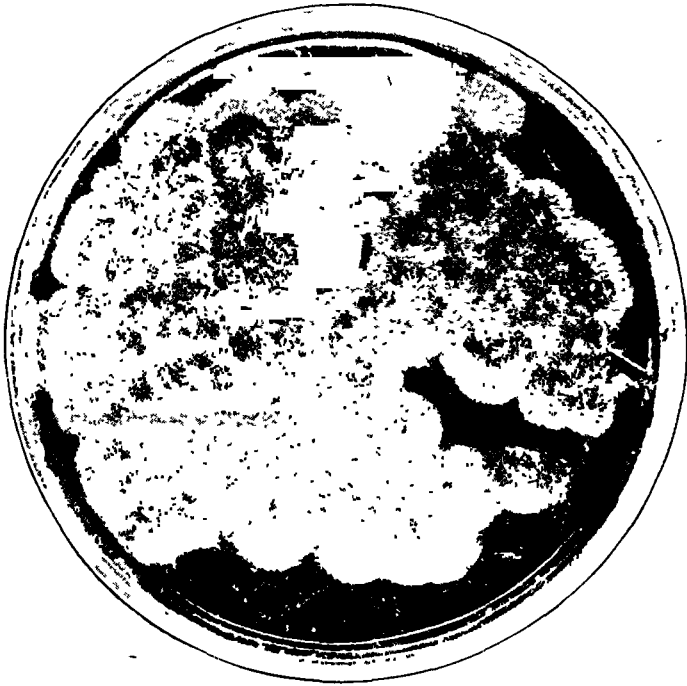


Fig. 5.—A colony of *C. immitis* cultured on blood agar at 22 C. in a Petri dish. The moldlike growth of this organism and the well formed aerial hyphae are evident.

illustrates the spore-filled "capsules" of the organism *C. immitis*. Figure 5 shows a ten day growth of the culture on blood agar at 22 C. and demonstrates the development of aerial hyphae.

Sulfanilamide was administered to the patient from October 10 through November 6, in doses of 45 to 90 grains (3 to 6 Gm.) daily. The values for concentration of sulfanilamide and hemoglobin in the blood and leukocyte counts are shown in table 2. Roentgen irradiation was administered over the ankles of the patient from October 23 to November 9, as indicated in table 3. His course in the hospital was essentially afebrile.

Roentgenograms of the ankles made on November 15 showed no significant change from those made when the patient was first admitted to our care. At the time of his dismissal his condition seemed to be essentially unaltered.

TABLE 2.—*Values for Concentration of Sulfanilamide and Hemoglobin in the Blood and Leukocyte Counts for a Patient Suffering from Coccidioidal Granuloma Treated with Sulfanilamide and Roentgen Irradiation \**

Date, 1940		Sulfanilamide in Blood, Mg. per 100 Cc.	Hemoglobin, Gm. per 100 Cc.	Leukocytes per Cu. Mm.
October	November			
2	..	....	12.7	11,300
11	..	....	14.6	6,200
14	..	....	15.9	6,700
17	..	8.2	13.2	8,400
19	..	....	15.0	9,900
21	..	10.4	12.4	8,200
23	..	....	13.5	.....
24	..	9.0	....	.....
26	..	12.0	....	8,600
28	..	11.6	....	4,700
30	..	10.4	....	7,700
	1	10.2	....	6,600
	2	13.8	....	.....
	4	11.4	9.3	6,600
	6	10.8	....	8,000
	14	....	10.0	14,500

\* The schedule and record of roentgen therapy appear in table 3.

TABLE 3.—*Record of Roentgen Therapy for a Patient Suffering from Coccidioidal Granuloma*

Date, 1940		Kilovolts	Distance, Inches	Milli- amperes	Filtration (Aluminum)	Time, Minutes
October	November					
23	..	130	16	6	6 mm.	5
28	..	130	16	6	6 mm.	5
	1	130	16	6	6 mm.	5
	5	130	16	6	6 mm.	5
	9	130	16	6	6 mm.	5

TABLE 4.—*Differential Diagnosis of Coccidioidal Granuloma, Blastomycosis and Torulosis \**

Organism	Disease Caused	Histologic Considerations				Distribution of Lesions
		Histologic Reaction	Cellular Products	Bud- ding	Spores	
C. immitis	Coccidioidal granuloma	Acute, with polymorpho-nuclear leuko-cytes	None	Never	Always	Skin; generalized (especially lungs)
Blastomyces dermatitidis †	Blastomycosis	Acute, with polymorpho-nuclear leuko-cytes	None	Always	Never	Skin; generalized (especially lungs)
Debaromyces neoformans	Torulosis	Mild; chronic	Mucoid material	Some-times	Never	Usually brain, meninges
Organism	Disease Caused	Laboratory Considerations			Pathogenicity (For Animals)	
		Organisms in Culture				
		Mycellums	Ascospores	Colonies		
B. dermatitidis	Blastomycosis	Always	Never (?)	Dry, "fuzzy"	Slight or absent	
C. immitis	Coccidioidal granuloma	Always	Never	Dry, "fuzzy"	Marked for all labora-tory animals	
D. neoformans	Torulosis	Never	Recently demon-strated	Moist (mucoid)	Marked for rats and mice, slight for guinea pigs (principally lesions in the brain)	

\* Adapted, with minor changes, from W. McK. Craig, M. B. Dockerty and S. W. Harrington: Intravertebral and Intrathoracic Blastomycoma Simulating Dumb-Bell Tumor, South. Surgeon 9: 759-766 (Oct.) 1940.

† The fungus *Zymonema dermatitidis* has been named by some as the etiologic agent in blastomycosis. However, because absolute proof is lacking, Henricl and others expressed themselves to be in favor of retaining this older term, manifestly inaccurate but justified on the basis of usage.



## COMMENT

Blastomycosis, coccidioidomycosis and torulosis are at times difficult to differentiate. Table 4 (modified from Benham) has been included here for those who, like us, encounter these conditions only occasionally. It presents briefly the chief laboratory and histologic points in the differential diagnosis of coccidioidal granuloma, blastomycosis and torulosis.

## SUMMARY

The phenomena of coccidioidomycosis are briefly reviewed, and a case is reported of coccidioidomycosis of the ankle joints, in which chemotherapy with sulfanilamide alone and in combination with roentgen irradiation proved to be ineffective. Failure of sulfanilamide to act as a fungicide for *C. immitis* in vitro has been recorded.

# EDEMA WITH UNEXPLAINED HYPOPROTEINEMIA

A SYNDROME OF DEFECTIVE FORMATION OF SERUM PROTEINS  
IN THE ABSENCE OF "LOSS AND LACK" OF PROTEIN  
AND DEMONSTRABLE HEPATIC DISEASE

DAVID A. RYTAND, M.D.

SAN FRANCISCO

Until lately the state of hypoproteinemia has been explained as the consequence either of loss of body protein, such as occurs in nephritis, or of the lack of dietary protein. Recently Bloomfield,<sup>1</sup> Melnick and Cowgill<sup>2</sup> and others have shown the inadequacy of this "loss and lack" theory and have pointed to defective formation of serum proteins as a factor in the reduction of serum protein concentration.

Some of the evidence favoring the hepatic origin<sup>3</sup> of the plasma proteins derives from reported cases<sup>4</sup> of hepatic disease with hypoproteinemia apparently due to defective protein formation (without loss of ascitic fluid). In cases of nephritis such impairment of protein formation is more difficult to demonstrate, even though the serum protein concentration may decline in some patients who lose only a few grams of protein in the urine, while in other patients (and in rats after subtotal nephrectomy<sup>5</sup>) relatively huge amounts of protein may be lost without material alteration of the amount of protein in the serum.

This great variation in the tolerance of different persons to protein loss suggests the possible existence of a state with defective formation of serum proteins in which edema might occur with otherwise unexplained

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From the Department of Medicine, Stanford University School of Medicine.

1. Bloomfield, A. L.: The Effect of Restriction of Protein Intake on the Serum Protein Concentration of the Rat, *J. Exper. Med.* **57**:705-720 (May) 1933.

2. Melnick, D., and Cowgill, G. R.: The Problem of Hypoproteinemia, *Yale J. Biol. & Med.* **10**:49-63 (Oct.) 1937.

3. Madden, S. C., and Whipple, G. H.: Plasma Proteins: Their Source, Production and Utilization, *Physiol. Rev.* **20**:194-217 (April) 1940.

4. (a) Myers, W. K., and Taylor, F. H. L.: Hypoproteinemia Probably Due to Deficient Formation of Plasma Proteins: A Study of One Case, *J. A. M. A.* **101**:198-200 (July 15) 1933. (b) Thompson, W. H.; McQuarrie, I., and Bell, E. T.: Edema Associated with Hypogenesis of Serum Proteins and Atrophic Changes in the Liver, *J. Pediat.* **9**:604-619 (Nov.) 1936. (c) Weech, A. A.: Nutritional Edema, *Internat. Clin.* **2**:223-248 (June) 1936.

5. Ludewig, S., and Chanutin, A.: Experimental Renal Insufficiency Produced by Partial Nephrectomy: IX. Blood Plasma Protein Values for Control and Partially Nephrectomized Rats Fed Diets Containing Dried Extracted Beef Muscle, *Arch. Int. Med.* **61**:847-853 (June) 1938.

hypoproteinemia, without loss or lack of protein and without hepatic or renal disorder. Such a syndrome seems actually to occur; 4 cases have been reported, and some detailed observations on a fifth case are presented in this paper.

#### REPORT OF A CASE

E. M. B., an American housewife aged 24, entered Lane Hospital June 10, 1940 for study of swelling of her legs.

*History.*—Her father had died at the age of 47 of coronary arteriosclerosis; her mother, aged 45, was well. Six brothers and sisters were alive and well.

The patient had always lived in Oregon or California. She had had measles, chickenpox and diphtheria in early childhood. When she was 6 years old, a fall had resulted in partial paralysis of the "entire left side," with full recovery in six months; in 1931, when the patient was 15 years old, an adenotonsillectomy had been performed. She had never been pregnant and had been entirely healthy up to the time of the illness reported here, which began eight years ago, in 1933.

In March 1934 she visited another hospital because of swelling and redness of the left leg of two weeks' duration. The record made at that time notes that both legs had been swollen for a year. There were no other symptoms. Examination then revealed soft pitting edema of the left leg to the knee and less edema of the right leg halfway to the knee. There was a tender red area just above the left ankle, but veins, lymphatics and lymph nodes were not tender. Her oral temperature on admission was 100 F.; it dropped rapidly to 98 F. and stayed normal during eighteen days of hospitalization. The white blood cell count was 7,700 per cubic millimeter, and a roentgenogram of the left leg was normal. Treatment consisted of rest in bed and application of hot compresses; the edema disappeared.

Soon, however, the swelling returned in both legs, without constitutional symptoms; at first it was present only toward night, but later the legs were swollen all day long, and the patient again noted that pressure left a deep pit. At that time the edema was cyclic, with no apparent correlation with menses or anything the patient did (except that it was perhaps worse when she was mentally upset and better when calm); the edema would be present one or two months and absent for the same length of time. Later it was present always but varied in intensity; sometimes even the thighs and the lower part of the back were swollen, sometimes only the ankles.

Early in 1939 she sought relief at another hospital. Nothing was found but pitting edema. The blood count and the urine were normal. More pertinent were a normal reaction to the rose bengal test and a total plasma protein concentration of 3.95 Gm. per hundred cubic centimeters, with 2.68 Gm. of albumin and 1.27 Gm. of globulin. Digitalis and a low salt diet were prescribed. However, the edema persisted; in April 1940 she was again hospitalized, but nothing was noted save edema, a normal Takata-Ara reaction and a total serum protein concentration of 3.80 Gm. per hundred cubic centimeters. She finally entered Lane Hospital for study on June 10, 1940.

*Dietetic History.*—During her high school years (1930-1934) the patient ate for breakfast a large dish of cereal, 2 slices of buttered toast, fruit and a pint (473 cc.) of milk, with an egg every other day. At lunch she had vegetables, potato, fruit and bread or fruit and sandwiches. Dinner consisted of salad, potato, vegetables, bread and dessert; never liking meat well, she ate it (usually lamb or lamb chops) only twice a week. Between meals she ate apples, candy,

crackers and cheese in moderation. From 1935 to 1939 she quit taking milk at breakfast (because of indigestion) but had ice cream or a milk shake at night; otherwise the diet was about the same as before. So from 1930 to 1939 the diet was adequate; its protein content ranged from perhaps 60 to 100 Gm. daily, averaging about 65 to 70 Gm.

A few months after discovery of the low plasma protein concentration on Feb. 6, 1939, a physician prescribed a high protein diet. The patient added to the aforementioned diet a pint and a half (700 cc.) of milk daily, 6 eggs a week, bacon (3 strips) twice a week, a half pound (227 Gm.) of cheese weekly, meat sandwiches at noon every other day and 2 lamb chops (or a small steak, 2 slices of liver or a piece of ham) each night. The diet has raised the intake of protein to 100 to 120 Gm. a day for the past year.

*Physical Examination.*—The patient did not appear ill; she was well developed and a bit obese, 170 cm. in height and 82.0 Kg. in weight (later 75.7 Kg. in remission). The head and neck were normal; there was no venous distention, and the eyelids were not swollen. The lungs were clear. The heart was not enlarged, and its sounds were normal. The cardiac rate was not rapid (56 per minute under basal conditions), and the blood pressure was 125 systolic and 75 diastolic, measured in millimeters of mercury. There was no fever. The abdomen was normal; neither liver nor spleen was palpable. There was no jaundice, and no spider angiomas were present. Pelvic, rectal and neurologic examinations yielded nothing abnormal. There was marked soft pitting edema of both lower extremities (a little more on the right side) and of the back as high as the level of the third lumbar vertebra. The skin was dusky red over both tibias (each area measuring 10 by 25 cm.), and these regions were tender, but there were no tender or palpable cords over the courses of the veins or the lymphatics of the leg. Lymph nodes were not enlarged.

*Laboratory Studies.*—The blood count showed 5,450,000 erythrocytes and 8,000 leukocytes per cubic millimeter. There was 15.8 Gm. of hemoglobin per hundred cubic centimeters (92 per cent Sahli). The erythrocytes were a little thicker (2.4 microns) than normal and averaged only 6.5 microns in diameter, with none over 7.5 microns; the mean corpuscular volume (80.1 cubic microns) and the mean corpuscular hemoglobin content (28.9 micromicrograms) were at the lower limit of normal, while the mean corpuscular hemoglobin concentration was normal (36.1 per cent). There were 167,400 reticulocytes (3.1 per cent of the erythrocytes) and 405,000 platelets per cubic millimeter. Fragility to a hypotonic solution of sodium chloride was normal, hemolysis starting at 0.46 per cent and ending at 0.24 per cent. The differential white count revealed 7 per cent eosinophils (560 per cubic millimeter), 1 per cent basophils, 8 per cent monocytes, 16 per cent lymphocytes and 68 per cent polymorphonuclear neutrophils (16 per cent banded and 52 per cent segmented). The clotting time of the whole blood was four and a half minutes and that of plasma five minutes; the clot retracted normally. The sedimentation rate was only 3 mm. in an hour.

The results of routine urinalysis were negative, and an Addis sediment count failed to reveal any casts or red blood cells and disclosed only 2,000,000 white blood and epithelial cells in a twenty-four hour specimen; there was only the normal immeasurably small amount of protein. The amount of urobilinogen in the urine was normal.

The stool was soft and brown, and did not contain any occult blood, parasites, fat, starch granules or muscle fibers; there were rare vegetable cells. Nitrogen in the stool was less than 1 Gm. per day.

The basal metabolic rate was —2.3 per cent. An electrocardiogram showed only left axis deviation. The highest ten minute volume of gastric juice secreted after the administration of histamine was 37 cc., with 22 degrees free hydrochloric acid and 31 degrees total acid. Roentgenograms of the chest and of the kidneys after intravenous injection of diodrast were normal. The Wassermann reaction of the blood was negative, as was the cutaneous reaction to tuberculin in a dilution of 1:10,000.

There was no retention of bromsulphalein (5 mg. per kilogram of body weight) in the blood thirty minutes after injection. Two grams of sodium benzoate was injected intravenously; from the urine voided during the succeeding two hours 1.12 Gm. of hippuric acid (as benzoic acid) was recovered (a normal rate of excretion). The icterus index was 1; the direct van den Bergh reaction was negative, and the concentration of bilirubin was only 0.03 mg. per hundred cubic centimeters.

The concentrations of various substances in the blood, expressed in milligrams per hundred cubic centimeters, were as follows: dextrose, 84 (three hours after

TABLE 1.—*Nitrogen Balance of a Patient with Edema and Unexplained Hypoproteinemia*

Date, June 1940	Daily Intake of Nitrogen, Gm.	Daily Output of Nitrogen, Gm.			Balance,* Gm.
		Urine		Stool, Total Nitrogen	
		Urea Nitrogen	Total Nitrogen		
18.....	24.1	14.5	....	...	+7.6
19...	21.4	12.3	..	...	+7.1
20..	22.7	14.0	15.4	0.4	+6.7
21..	17.8	14.0	14.8	1.7	+1.8
22.....	21.1	13.2	....	0.8	+5.9
23.....	16.6	12.6	....	...	+2.0
24.....	16.5	8.9	..	...	+5.6
Mean....	20.0	12.8	. ..	0.97	+5.2

\* The daily loss of 1 Gm. of nitrogen in the stools and 1 Gm. of nonurea nitrogen in the urine is assumed.

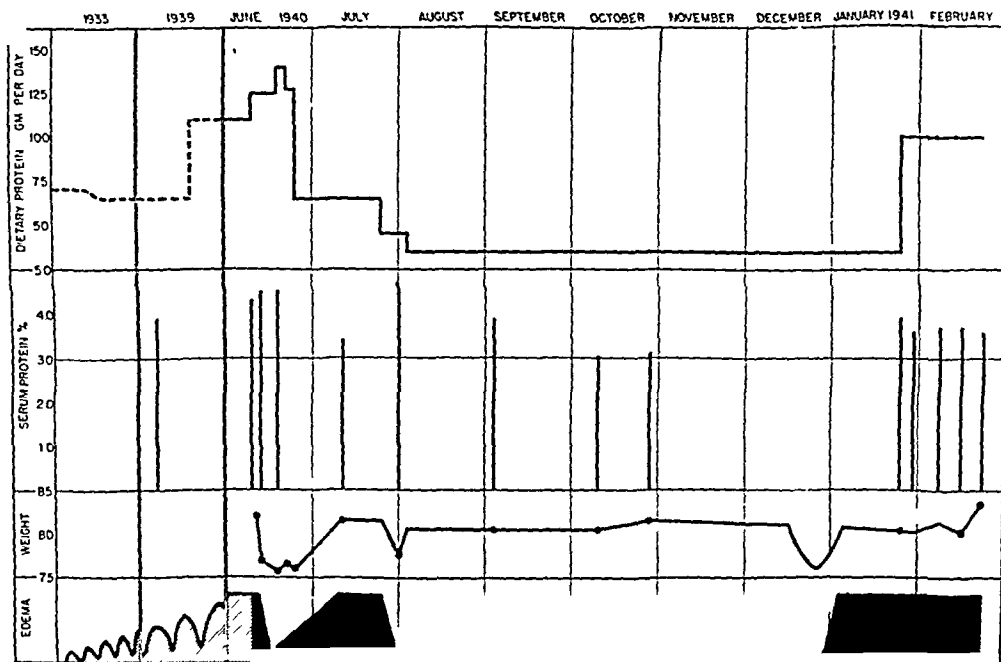
breakfast); calcium, 7.1 (serum); inorganic phosphorus, 3.3 (serum); phosphatase (and amylase), normal; cholesterol, 145; uric acid, 1.3 (serum) and 2 (whole blood); amino acid nitrogen 4.0 (serum) and 6.2 (whole blood), and urea, 25.5. The blood volume was 6,260 cc. (82 cc. per kilogram of body weight, 3.3 liters per square meter of body surface), and the plasma volume 3,380 cc. Of injected congo red, 80 per cent remained in the serum at the end of one hour.

The total serum protein was determined thirteen times in nine months and was found to vary from 3.00 to 4.68 Gm. per hundred cubic centimeters (average 3.86 Gm.). Fractionation of the serum with salts once showed the concentration of albumin and globulins to be 2.3 and 1.3 Gm. per hundred cubic centimeters, respectively (total 3.6 Gm.). On another occasion, with a total serum protein concentration of 4.49 Gm. per hundred cubic centimeters, electrophoretic analysis by Dr. Eloise Jameson yielded the following results in terms of grams of protein per hundred cubic centimeters of serum; albumin, 2.83; alpha globulin, 0.27; beta globulin, 0.70; gamma globulin, 0.69, and total globulins, 1.66. On the two occasions the albumin-globulin ratio was 1.70 and 1.77. The concentration of fibrinogen was 0.29 and 0.30 Gm. per hundred cubic centimeters of plasma, respectively.

*Course of Illness.*—As later events indicated, the patient entered the hospital at the start of a spontaneous partial remission, with a serum protein concentration of 4.3 to 4.6 Gm. per hundred cubic centimeters. The edema promptly diminished from the legs and the lower part of her back as her weight fell from 82.0 to 75.7 Kg.

Her daily diet contained about 150 Gm. of protein and 2,340 calories; after a week the observations on nitrogen balance were made as recorded in table 1. While the data are incomplete, they show a positive nitrogen balance, in spite of the appearance of herpes zoster (afebrile) at the left sixth thoracic segment on June 17. She left the hospital June 25, weighing 75.9 Kg.

When examined in the outpatient department two weeks later she again weighed 81.5 Kg. and was grossly edematous, with a serum protein concentration of 3.42 Gm. per hundred cubic centimeters, in spite of the high protein diet and large doses of thiamine hydrochloride.



The degree of edema, weight, total serum protein concentration and protein intake for E.M.B. Note three spontaneous partial remissions and the absence of any correlation between protein intake and the serum protein concentrations or remissions.

At this time she was plagued by family and financial troubles, went on 'relief' and could obtain an average of only 35 Gm. of protein in her daily diet (bacon, 1 egg, toast, soup, potatoes, lettuce, carrots and buttered bread, with milk twice a week). Yet she returned at the end of July almost free of edema, weighing 77.6 Kg. and with a serum protein concentration of 4.68 Gm. per hundred cubic centimeters (figure).

In October she took amino acid powder by mouth, with no effect. A third spontaneous partial remission occurred in December but was not observed. For eighteen days in January and February she took her meals under observation in the hospital, eating food high in vitamins and averaging 100 Gm. of protein and 2,000 calories daily; her weight increased from 80.6 to 83.4 Kg., without obvious

change in the amount of edema, while the serum protein concentration fell slightly (3.9 to 3.6 Gm. per hundred cubic centimeters).

Throughout these nine months she underwent observation rather grudgingly and was unwilling to permit such therapeutic attempts as a low salt diet, administration of diuretics or transfusions; therefore the data just reported represent practically the spontaneous course of this disorder.

#### COMMENT

The first clinical problem was to determine the cause of the edema; it was undoubtedly hypoproteinemia. Then an unsuccessful search was instituted for known causes of hypoproteinemia (table 2). There was

TABLE 2.—*Physiologic Causes of Hypoproteinemia*

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A. Loss and destruction of body protein	
I. Urine	(Bright's disease)
II. Ascitic fluid	(cirrhosis with paracenteses)
III. Tissue	(cachexia)
IV. Fetus	(pregnancy)
B. Retarded formation of serum protein	
I. Lack of dietary protein	
(a) Absolute total dietary insufficiency	
(1) Starvation	
(2) Pyloric obstruction	
(3) Diarrhea	
(b) Relative total dietary insufficiency	
(1) Pregnancy	
(2) Hyperthyroidism	
(3) Diabetes mellitus	
(c) Dietary protein deficiency	
(1) Low protein diet	
(2) Pancreatic disease	
II. Altered states of the body	
(a) Normal	
(1) The newborn	
(b) Abnormal	
(1) Hepatic disease	
(2) Bright's disease	
(3) Beriberi	
III. Unexplained	

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no loss of body protein in the urine or in ascitic fluid; no destruction (see urinary nitrogen loss, table 1), as in cachexia, and no sidetracking, as in new tissue growth. There was neither absolute lack of food, as in starvation, vomiting or diarrhea, nor relative lack as in pregnancy, hyperthyroidism or diabetes mellitus. There was no specific dietary deficiency of protein (except, fortunately, while the patient was under observation; even then it did not prevent two remissions) and no loss of nitrogen in the stool through any defect of protein absorption, as in pancreatic disease.

Beriberi was excluded by the absence of neuritis and cardiac disturbances and by the failure of thiamine to induce a remission. Bright's disease was not present. Hepatic disease was, of course, impossible to exclude, but its presence was improbable for the following reasons: In the history there were no etiologic factors, such as alcoholism; the patient

had never been jaundiced, and after eight years of illness any disease of the liver should have been fairly obvious if present. Furthermore, physical examination failed to reveal jaundice, spider angiomas or ascites; neither the liver nor the spleen was palpable. Finally, laboratory studies showed a low icterus index and concentration of bilirubin in the blood, a normal amount of urobilinogen in the urine, normal results of the bromsulphalein and hippuric acid tests, normal plasma coagulation time and small erythrocytes.

The hypoproteinemia was not due to mere dilution by an increased blood plasma volume, for measurement revealed a normal volume (incidentally, the congo red method used indicated the absence of amyloidosis). It was not familial, or at least no other members of the family were edematous. A final diagnosis of hypoproteinemia due to an unexplained retarded formation of serum protein was made, and interest then turned to a study of the blood proteins themselves.

Those plasma proteins concerned with blood coagulation (and formed in the liver—fibrinogen and prothrombin) were normal. Hemoglobin was also normal in concentration. Albumin and the serum globulins were reduced proportionately, so that the albumin-globulin ratio was normal. By comparing the protein fractions obtained by electrophoresis with the most recently published normal standards,<sup>6</sup> one may calculate the total plasma protein of the patient at 73 per cent of normal; albumin, at 70 per cent; fibrinogen, at 78 per cent and globulins, alpha, beta and gamma, at 59, 82 and 92 per cent, respectively. (These changes are not similar to those found<sup>6</sup> in cases of "nephrosis," cirrhosis, heart failure, etc.) While the usual level of total serum protein was about 3.9 Gm. per hundred cubic centimeters, it once dropped to 3.0 Gm. and twice was observed to rise to 4.5 and 4.7 Gm., respectively. This behavior could not be correlated with any other changes.

In a search for other abnormalities the formed elements of the blood were of interest. Certain rather subtle changes, easily overlooked in casual examination, were found: eosinophilia, reticulocytosis and slight increase in thickness but decrease in diameter of the erythrocytes, with volume at the lower limits of normal. No disease of allergic origin or parasite was found (and no liver extract given) which might explain the eosinophilia. The latter has been described,<sup>7</sup> however, in association with chronic nephritis (though not necessarily with edema), and attempts have been made<sup>8</sup> to link eosinophils with protein metabolism.

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6. Leutscher, J. A., Jr.: Electrophoretic Analysis of the Proteins of Plasma and Serous Effusions, *J. Clin. Investigation* **20**:99-106 (Jan.) 1941.

7. Kollert, V., and Paschkis, K.: Das weisse Blutbild bei Nephritis, *Ztschr. f. klin. Med.*, **112**:275-288, 1930.

8. Hall, I. W.: Eosinophiles and Homologous Proteins, *J. Path. & Bact.* **40**:319-322 (March) 1935.



I know of an unreported case of starvation edema in which during recovery the eosinophils inexplicably rose to 25 per cent of 12,700 leukocytes.<sup>9</sup> As to the reticulocytosis and the erythrocyte shape, a fragility test yielded a normal result. The amount of urobilinogen excreted in the urine was normal, and the blood level of bilirubin was not elevated.

As a matter of fact, the icterus index was only 1, and the level of bilirubin in the blood was as low as 0.03 mg. per hundred cubic centimeters. Uric acid in the serum was also at the lower limits of normal (1.3 mg. per hundred cubic centimeters). With clinical attention centered on jaundice and gout, not much seems to be known concerning decreased concentrations of bilirubin and uric acid. Both have been said to be adsorbed by serum albumin<sup>10</sup> and so might be expected to be low in the hypoproteinemic state, just as serum calcium is low. But the experiments with albumin adsorption of bilirubin were concerned with high concentrations of bilirubin, and it has since been observed that the amount of bilirubin in the blood need not be decreased in all cases of hypoproteinemia.

A decrease in blood amino acid nitrogen, such as has been noted at times in cases of "nephrosis,"<sup>11</sup> was not found. Cholesterol was somewhat lower than usual in the blood (145 mg. per hundred cubic centimeters), another bit of evidence against the theory that it rises in patients with nephritis and associated edema to increase the plasma colloidal osmotic pressure.

Finally, table 3 presents a comparison of the findings in this case with those in 4 cases of a similar condition previously reported.<sup>12</sup> The patients were all young, and all but 1 were women. The duration of illness is as long as eight years (possibly twelve years in Johansen's case, in the difficultly decipherable report of which nothing is found about the necropsy prematurely reviewed<sup>3</sup>). One patient was "infantile," 1 had a uterine fibroid and 1 had been edematous in a "normal" pregnancy eight years before study but not edematous in a pregnancy three years later.

The serum protein concentration was determined repeatedly for 4 patients: The averages for each were similar, 3.8, 3.9, 4.1 and 4.3 Gm.

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9. Lewis, J. K.: Personal communication to the author.

10. Bennhold, H.: Ueber die Vehikelfunktion der Serumeiweisskörper, *Ergebn. d. inn. Med. u. Kinderh.* **42**:273-375, 1932.

11. Farr, L. E., and MacFadyen, D. A.: Hypoaminoacidemia in Children with Nephrotic Crises, *Am. J. Dis. Child.* **59**:782-792 (April) 1940.

12. (a) Cope, C. L., and Goadly, H. K.: Study of a Case of Idiopathic Hypoproteinaemia, *Lancet* **1**:1038-1040 (May 4) 1935. (b) Johansen, A. H.: Hypoproteinemia, *Acta path. et microbiol. Scandinav.*, 1938, supp. 37, pp. 272-289. (c) Binger, M. W., and Keith, N. M.: General Edema of Indeterminate Etiology: Report of Three Cases, *J. A. M. A.* **109**:1-6 (July 3) 1937.

per hundred cubic centimeters. The similarity is even more striking in the case of serum albumin, values for this averaging 2.5, 2.5, 2.6 and 2.6 Gm. per hundred cubic centimeters. The concentrations of the serum globulins were 1.3, 1.5, 1.6 and 1.9 Gm. per hundred cubic centimeters. The albumin-globulin ratios were all normal, 1.5, 1.6, 1.7, 1.8 and 2.1. The concentrations of fibrinogen were normal or slightly elevated.

While the average concentrations of total protein were similar when values for different patients were compared, each person presented striking spontaneous fluctuations (0.9 to 3.1 Gm. per hundred cubic centimeters) of 20 to 80 per cent of his own mean value. These were mirrored in the 6.4 and 7.7 kilogram variations in weight of the 2 subjects who received no diuretics. These changes in the serum protein levels were not related to the dietary protein; intakes of 1.5 to over 2.5 Gm. of protein per kilogram of body weight per day did not increase the concentrations of serum protein, even though the nitrogen balance was shown to be positive for 3 patients.

None lost protein in the urine or by other routes, and at least 2 did not lose nitrogen excessively in the stools.

Each patient had at least one test of hepatic function with normal results; 3 were shown not to be icteric, and in the present case a battery of tests and circumstances rather conclusively excluded hepatic disease. In no case could it be shown that the state of hypoproteinemia had damaged the liver<sup>13</sup> (the patient studied by Myers and Taylor<sup>4a</sup> had a history of alcoholism).

Red blood cell counts and hemoglobin concentrations were normal for all 5 patients, and for 2 the white count given was normal (but see the report for further studies of the blood cells in the present case). The Wassermann reaction of the blood was negative in all cases, the tuberculin reaction in 3 and the basal metabolic rate in 4. There was gastric anacidity in 1 case (normal secretion in 3).

As expected, the oncotic pressure of the serum was reduced in the 1 patient for whom it was measured, and in another the protein concentration in the edema fluid was only 0.14 Gm. per hundred cubic centimeters.

The blood volume was normal in both cases in which it was studied. The concentrations of nonprotein nitrogen in the blood were all normal; those of cholesterol were all normal or low, and those of serum calcium were at times surprisingly normal (at other times low, as expected).

Of further interest may be the slow sedimentation rate (1 mm. per hour) and the low concentration of bilirubin (under 1.0 mg. per hundred

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13. Elman, R., and Heifetz, C. J.: Experimental Hypoalbuminemia: Its Effect on the Morphology, Function, and Protein and Water Content of the Liver, *J. Exper. Med.* **73**:417-430 (March) 1941.

TABLE 3.—Comparison of Data in Five Cases of Unexplained Hypoproteinemia

	Author			
	Ryland	Cope and Goudly <sup>12a</sup>	Johansen <sup>12b</sup>	Binger and Keith <sup>12c</sup> (case 2)
Age of patient, years.....	24	20	25	35
Sex .....	Female	Male	Female	Female
Duration of edema, years.....	8	1½	7½	3
Weight, Kg. ....	75.7 to 83.4	63.6 to 70.0	....	66.9 to 74.0
Total serum protein: Mean, Gm. per 100 cc.....	3.86	4.32	3.26	3.91
Range, Gm. per 100 cc.....	3.00 to 4.68	3.70 to 4.64		2.7 to 5.8
Serum albumin: Mean, Gm. per 100 cc.....	2.56	2.63	2.10	2.63
Range, Gm. per 100 cc.....	2.30 to 2.83	1.94 to 3.13		1.4 to 4.0
Serum globulins: Mean, Gm. per 100 cc.....	1.48	1.69	1.16	1.28
Range, Gm. per 100 cc.....	1.30 to 1.66	1.51 to 1.89		1.0 to 1.9
Albumin-globulin ratio: Mean.....	1.73	1.58	1.81	2.08
Range .....	1.70 to 1.77	1.09 to 2.07		1.0 to 2.9
Fibrinogen: Mean, Gm. per 100 cc.....	0.29	0.64	0.37	0.56
Range, Gm. per 100 cc.....	0.29 to 0.30	0.45 to 0.80		0.43 to 0.68
Loss of protein.....	None	None	None	None
Stool nitrogen, Gm. per day.....	0.97	1.7	.....	.....
High protein diet without benefit, Gm. per Kg. per day.....	1.5	2.6		1.6
Nitrogen balance .....	Positive	Positive	"Normal"	.....
Tests of hepatic function				
Levulose tolerance .....	.....	Normal	.....	.....
Galactose tolerance .....	.....	.....	Normal	.....
Congo red (amyloid).....	Normal	.....	.....	.....
Takata-Ara .....	Normal	.....	.....	.....
Rose bengal excretion.....	Normal	.....	.....	.....
Bromsulphalein excretion .....	Normal	.....	.....	.....
Hippuric acid excretion .....	Normal	.....	.....	Normal
Icterus index, units .....	1.0	.....	.....	.....
Serum bilirubin, mg. per 100 cc.....	0.03	.....	.....	.....
Urinary urobilinogen .....	Normal	.....	.....	.....
Plasma clotting time, minutes.....	5 (normal)	.....	.....	1.0
Blood clotting time, minutes.....	4½	.....	.....	.....
Hemoglobin, Gm. per 100 cc.; per cent Sahli.....	15.78; 92	18.4; 107	15.9; 93	13.8; 81
				14.9; 87



cubic centimeters; icterus index, 2.0) in the blood in the case reported by Myers and Taylor,<sup>4a</sup> which were similar to the findings in my case.

Treatment (other than with diuretics<sup>12c</sup>) was unsatisfactory. Amino acid feeding was not beneficial in 2 cases, nor were high protein diets in any of 4. Only 1 patient was given blood transfusions, with temporary relief (note a remission for one month after transfusion in a child with hepatic disease<sup>4b</sup>).

As to any bearing on the site of production of the serum proteins, the changes observed in all these cases, especially those (abnormal size of erythrocytes, reticulocytosis, eosinophilia and perhaps the low concentrations of uric acid and bilirubin in the serum) in the case reported here, suggest not the liver<sup>3</sup> but the bone marrow<sup>14</sup> or the reticulo-endothelial system. A biopsy of the bone marrow yielded "normal" results in 1 case.

#### SUMMARY

The case is reported of a young woman who was edematous for eight years because of hypoproteinemia, for which none of the usual causes appeared to be present. Four previously reported cases of a similar condition are summarized and compared.

#### CONCLUSIONS

There is a syndrome in which the formation of serum proteins is inexplicably defective. Such a defect also plays a part in those patients with chronic nephritis in whom hypoproteinemia occurs and perhaps in patients with other disorders in which the maintenance of a normal concentration of serum proteins imposes unusual strain on the mechanism. The syndrome here described may be but an exaggerated expression of the varying abilities of different persons to form serum protein; while ordinarily loss of protein or nitrogen is required to unmask such differences, here the defect appears spontaneously.

Although the liver undoubtedly forms some of the plasma proteins, the evidence discussed here suggests bone marrow (or the reticulo-endothelial system) as another site.

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14. Sabin, F. R.: Cellular Reactions to a Dye-Protein with a Concept of the Mechanism of Antibody Formation, *J. Exper. Med.* **70**:67-82 (July) 1939.

# DESTRUCTIVE OSSEOUS LESIONS IN EARLY SYPHILIS

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Early in the course of acquired syphilitic infection, spirochetes are widely disseminated throughout the body tissues, including those of the bony skeleton.<sup>1</sup> Yet despite the fact that bone, together with its periosteum and marrow cavity, is known to harbor virulent organisms, the development of objective skeletal abnormalities during the early stages of the disease is comparatively rare. When the skeletal structures do become involved during early syphilis, the involvement is usually proliferative periostitis. More rarely destructive osteitis and osteomyelitis occur. It is with the latter lesions that this study is concerned.

In a series of approximately 10,000 cases of early syphilis observed in the Syphilis Division of the Medical Clinic and the wards of the Johns Hopkins Hospital over a twenty-two year period (1919-1940), 15 instances of destructive bone lesions (osteitis, osteomyelitis, osteoperiostitis) have been recognized. In view of the rarity of these conditions and the relative scarcity of existing information on the subject, we report these cases and summarize the available literature.

Because of its painful nature, skeletal syphilis was one of the first manifestations of the disease to be recognized, and lucid descriptions of characteristic osteocopic pains and bony swellings appear in the writings of many of the earliest syphilologists. Nevertheless, lacking the diagnostic facilities afforded by the roentgen ray, these early clinicians were unable accurately to differentiate proliferative periosteal lesions from those in which actual bone destruction had occurred. Swediaur,<sup>2</sup> for example, after describing "periostitis, exostoses and a corruption of the substance of the bone known as caries," asserted that

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1. Neisser, A.: *Beiträge zur Pathologie und Therapie der Syphilis*, Berlin, Julius Springer, 1911, p. 101.

2. Swediaur, F. X.: *Traité complet sur les symptômes, les effets, la nature et le traitement des maladies syphilitiques*, ed. 4, Paris, 1801, pp. 179-188.

TABLE 1.—Summary of Previously Reported Cases

Author	Date	Patient			Evidence of Early Syphilis			Skeletal Lesion		Associated Lesions and Conditions	Relation to Primary or Secondary Syphilis	Effect of Specific Treatment	Comment
		Race and Sex	Age, Yr.	Pri. Yr.	Sec. Yr.	Dark Field Examination	Sero-logic Reaction	Bone Involved	Type of Involvement				
Nitchew <sup>1</sup> (a)	1932	White ♂	22	+	+	—	+	Skull	Osteoperiostitis	Cutaneous and serologic relapse; anorexia and diarrhea	3 wk. after secondary	Symptomatic relief with a bismuth compound	Moderate constitutional reaction; symptoms followed treatment with nearsphenamine, during serologic and cutaneous relapse
(b)	1932	White ♀	23	—	+	..	+	Tibia	Osteoperiostitis	None	135 days after secondary	Symptomatic relief after 3 injections of a bismuth compound	Symptoms followed treatment with nearsphenamine, after serologic reversal
(c)	1932	White ♂	26	+	—	+	—	Tibia	Osteoperiostitis	None	105 days after primary	Symptomatic relief after 5 injections of a bismuth compound	Contact case b; symptoms followed treatment with nearsphenamine, started in seronegative primary stage
Gougerot, Mathieu and Jais <sup>2</sup>	1932	White ♂	55	—	+	..	+	Clavicle	Osteitis	None	40 days after secondary	Symptomatic relief and healing by roentgen examination after treatment with a bismuth compound	Pathologic fracture, which healed well after antisyphilitic treatment
Bloom <sup>3</sup>	1931	Negro ♀	20	—	+	..	+	Clavicle	Osteitis	Facial palsy	About 1 mo. after secondary	Symptomatic relief; arrest after 4 mo. treatment apparent in roentgenogram	Symptoms followed 2 injections of a bismuth compound and 1 of nearsphenamine
Tauber and Goldman <sup>10</sup>	1935	Negro ♂	38	+	—	+	+	Skull; tibia; clavicle; scapula	Osteitis	Macrocytic anemia; weight loss; reaction of spinal fluid positive for syphilis	Indefinite	Symptomatic improvement; improvement apparent in roentgenogram after 2 mo.	Lesions like those of multiple myeloma; spinal fluid positive; biopsy
Mandelbaum and Saperstein <sup>21</sup>	1936	White ♀	29	—	—	..	+	Skull; sternum	Osteoperiostitis	None	8 to 12 wk. after blood transfusion	Serologic reversal in 4½ mo.; healing apparent in roentgenogram after 16 mo.	Syphilis acquired by blood transfusion; no marked constitutional reaction

Burrows 20	1937	White ♂	28	+	—	+	+	Humerus; skull; radius; ulna; fibula	Osteoperiostitis	None	15 mo. after primary	None given after fracture; spontaneous healing	Pathologic fracture of humerus; other lesions asymptomatic and discovered on routine roentgen ray examination
Newman and Saunders 11	1938	White ♀	28	+	—	..	+	Skull; radius; ulna; humerus; tibia	Osteomyelitis	Severe myopathy; anemia	After secondary	Asymptomatic improvement after 4 injections of a bismuth compound, complete healing apparent in roentgenogram after 4 mo. treatment	Marked constitutional reaction, with myopathy and anemia, clearing with antisyphilitic treatment
Parina 12	1939	White ♂	29	+	+	N	+	Radius; ulna; skull; sternum; bones of hands and feet	Osteoperiostitis; osteitis	Cutaneous relapse; chancre; anemia	5 mo. after primary; return with cutaneous relapse	Symptomatic improvement; relapse; cure with further treatment; arrest apparent in roentgenogram after 2 wk.	Return of symptoms with secondary eruption and chancre redux; widespread lesions
Squires and Weiner 13 (a)	1939	White ♀	20	—	+	—	+	Skull	Osteoperiostitis	None	27 days before secondary	Herxheimer reaction positive; improvement visible in roentgenogram 10 wk. later; complete healing apparent 9 mo. later	Husband had early syphilis, with chancre and macular syphilid
(b)	1939	White ♀	49	—	+	..	+	Ulna	Osteoperiostitis	None	Not stated	Complete healing after 5 injections of a bismuth compound and 5 injections of nearsphenamine	Patient had condylomata lata and mucous patches, with a papulosquamous syphilid
Wile and Welton 14 (a)	1940	White ♂	33	+	—	—	+	Ribs; spine	Osteomyelitis	Alopecia; splenomegaly	4 mo. after primary	Symptomatic improvement after 6 injections of arsphenamine and a bismuth compound combined; complete healing apparent in roentgenograms 9 yr. later	Lesions resembling those of multiple myeloma; constitutional symptoms marked; symptoms followed 6 injections of arsphenamine; biopsy
(b)	1940	White ♀	23	+	+	..	+	Skull	Osteoperiostitis; focal osteomyelitis	Splenomegaly	About 1½ mo. after primary	Herxheimer reaction positive; rapid symptomatic improvement; roentgenograms normal 4 yr. later	No marked constitutional reaction; severe headache
Plan and Prazler 22	1940	Chinese ♂	8	—	+	..	+	Skull; tibia; fibula; humerus; radius; ulna	Osteomyelitis	None	5 wk. after blood transfusion	Herxheimer reaction; symptoms gone after 2 injections of neoarsphenamine; healing apparent in roentgenograms 2 mo. later	Kala-azar; syphilis acquired by blood transfusion; S. pallida recovered from blood



"no physician, however well versed in the art, is capable of stating whether a given tumefaction is a lesion of the periosteum or of the bone itself."

Although based on clinical observations alone, without benefit of roentgenography, the writings of Mauriac,<sup>3</sup> Lancereaux<sup>4</sup> and Wile and Senear<sup>5</sup> afford valuable clinical data on the frequency and the course of early osseous syphilis in general.

Supported by gross and microscopic postmortem evidence, the case report of Lancereaux<sup>4</sup> is perhaps the first accurate description of destructive osteitis in early syphilis. In this remarkable case, destructive lesions of the nasopalatine and the frontal bones supervened one year after the development of a labial chancre and characteristic manifestations of secondary syphilis (rash, mucous patches and alopecia). So extensive were the osseous changes that death from brain abscess occurred after perforation of the inner table of the skull. Microscopically, dissolution of bone and dense round cell infiltration were noted.

Since the introduction of the roentgen examination into clinical medicine, more and more case reports of destructive bone lesions in early syphilis have been recorded.<sup>6</sup> In surveying the available literature, we have been able to collect 15 cases, which are summarized in tabular form (table 1).

The case reports of Nitchew<sup>7</sup> are the first recorded observations to be supported by roentgenologic proof of bone destruction. This author expressed the belief that his 3 cases represented "precocious tertiary accidents," and, since in all 3 instances the onset of symptoms followed treatment with neoarsphenamine, he suggested that the arsenical therapy had altered the invasiveness of the spirochetes. In the same year Gougerot, Mathieu and Jais<sup>8</sup> reported a case in which pathologic fracture of the clavicle occurred forty days after the secondary eruption.

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3. Mauriac, C.: Sur les affections syphilitiques précoces du système osseux, *Gaz. d. hôp.* **45**:739, 1872.

4. Lancereaux, E.: Les ostéites syphilitiques, *Ann. de dermat. et syph.* **7**:261, 1886.

5. Wile, U. J., and Senear, F. E.: A Study of the Involvement of the Bones and Joints in Early Syphilis, *Am. J. M. Sc.* **152**:689, 1916.

6. It is of some interest in this connection that roentgenographically demonstrable bone lesions are not infrequent in the early stages of yaws, having been observed in 15 per cent of cases in one series (Turner, T. B.; Saunders, G. M., and Johnston, H. M.: Annual Report of the Jamaica Yaws Commission, Kingston, Jamaica, 1932).

7. Nitchew, L.: A propos des ostéo-périostites syphilitique précoces, *Ann. d. mal. vén.* **27**:600, 1932.

8. Gougerot, Mathieu and Jais: Fracture spontanée de la clavicule au début de la syphilis secondaire, *Ann. d. mal. vén.* **27**:31, 1932.

TABLE 2.—Summary of Cases from Johns Hopkins Hospital

Patient	Evidence of Early Syphilis				Bone Lesion		Associated Lesions and Conditions	Relation of Bone Lesion to Primary or Secondary Syphilis	Effect of Specific Treatment	Comment
	Race, Sex	Age, Yr.	Primary	Secondary	Dark-field Examination	Serologic Reaction				
					Bone Involved	Type of Involvement				
A. S.	White ♀	23	—	+	Tibia; fibula	Osteoperiostitis	Polyarthritides; serologic relapse; hepatitis	14 mo. after secondary	Relief after 6 injections of arsphenamine	Ossous lesions developed with serologic and hepatic recurrence after lapse following inadequate treatment
E. T.	Negro ♀	20	—	+	Humerus	Osteomyelitis	Polyarthritides	8 wk. before secondary	Improvement after injection of arsphenamine; complete relief after 8 injections	Serologic reversal after 4 injections of arsphenamine; complete healing apparent in roentgenograms after 4 mo. of treatment
J. C.	Negro ♂	35	+	+	Sternum	Osteoperiostitis	Asymptomatic syphilis of the central nervous system; orchitis	2 wk. after secondary	Improvement after 7 injections of arsphenamine; relapse also healed promptly	Trauma during secondary syphilis; lesion returned during treatment lapse
O. B.	Negro ♀	24	—	+	Skull	Osteoperiostitis	None	Before secondary	Improvement after 1 injection of arsphenamine	Serologic reversal after 5 mo. of treatment
A. T.	Negro ♂	24	—	+	Tibia	Osteoperiostitis	None	With secondary	Relief after 2 injections of arsphenamine	Follow-up observation incomplete
H. W.	Negro ♀	21	—	+	Skull	Osteitis	None	?	"Prompt relief"	Serologic reversal after 6 injections of neoarsphenamine; roentgenograms and physical findings normal after 7 yr.
A. W.	Negro ♀	17	..	+	Clavicle	Osteitis	Polyarthritides	1 mo. after secondary	Relief after 1 injection of arsphenamine	Subacute salpingitis; serologic tests negative and physical findings normal after 5 yr.; complete healing evident in roentgenograms
A. G.	Negro ♂	39	+	+	Skull	Osteoperiostitis	Arthralgia; iritis	With secondary	Relief after 3 injections of arsphenamine	Follow-up observation incomplete
G. N.	White ♂	25	—	+	Skull	Osteoperiostitis	None	11 wk. before secondary	Relief after 6 injections of neoarsphenamine	Extragenital chancre (?); secondary lesions developed during arsenical treatment; follow-up observation incomplete
G. R.	White ♂	35	+	—	Nasal bones	Osteitis	Anemia; polyarthritides	15 mo. after primary	Gradual healing after intensive treatment, including malaria	Malignant syphilis; marked constitutional reaction; episodes of leukopenia and agranulocytosis; biopsy
W. J.	Negro ♂	24	+	+	Skull	Osteoperiostitis	Arthralgia; uveitis	With secondary	Relief after 1 injection of arsphenamine	Follow-up observation incomplete
R. S.	Negro ♀	22	—	+	Skull	Osteoperiostitis	Arthritis of temporomandibular joint	5 wk. before secondary	Relief after 4 injections of arsphenamine	History of trauma; development of jaundice during arsphenamine treatment; roentgenogram normal 10 mo. later
S. B.	Negro ♀	30	—	+	Humerus; clavicle	Osteoperiostitis	None	?	Relief after 1 injection of arsphenamine	History of trauma; serologic reversal after 6 injections of arsphenamine
E. D.	Negro ♀	38	—	+	Clavicle	Osteoperiostitis	None	With secondary	Relief after 5 injections of neoarsphenamine	Follow-up observation incomplete
F. L.	White ♂	27	+	—	Facial bones; palate	Osteitis	Alopecia	8 mo. after primary	Gradual healing after intensive treatment	Malignant syphilis; treatment started during primary stage when serologic tests negative; progression during malaria; biopsy

In the case reported by Bloom,<sup>9</sup> symptoms also became manifest after the institution of antisyphilitic treatment. Symptomatic relief and demonstrable healing by roentgen rays followed further treatment. In retrospect, the case reported by Tauber and Goldman<sup>10</sup> as one of "syphilitic anemia with diffuse osteitis and superinfection" seems more probably an instance of skeletal involvement and anemia complicating early syphilis.

Newman and Saunders<sup>11</sup> emphasized the fact that marked constitutional evidences of toxicity may be present in association with early skeletal involvement. In the case they reported the patient, in addition to widespread bone lesions, had severe myopathy and anemia. Farina,<sup>12</sup> also, stressed the debilitating effect of the "malignant" type of early syphilis which developed in the patient whose case he reported.

The recent reports of Squires and Weiner<sup>13</sup> and Wile and Welton<sup>14</sup> indicated that toxemia is not an invariable component of the condition. In both these articles the diagnostic difficulties were stressed and the frequency with which the bones of the skull are involved was noted.

Our own series of 15 cases is also presented in tabular form (table 2). Illustrative case reports and roentgenograms are appended.

#### ANALYSIS OF CASES

An accurate estimate of the frequency of early skeletal syphilis is difficult to make. That it is more common than is generally recognized was demonstrated clinically by Wile and Seneal.<sup>5</sup> These authors carefully examined 165 patients with primary and secondary syphilis for objective skeletal abnormalities and were able to detect evidences of bone or joint involvement in 60, or 36 per cent, of the total. Many of these changes were minimal and would have been missed by a casual examiner. Their study gives no indication of the frequency with which destructive lesions were present, but it seems highly probable that if roentgenologic examination of the skeleton was included in such a study, instances of osteolytic processes would be noted.

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9. Bloom, P.: Destructive Osteitis and Facial Paralysis in Secondary Syphilis, *Arch. Dermat. & Syph.* **29**:940 (June) 1934.

10. Tauber, E. B., and Goldman, L.: Syphilitic Anemia with Diffuse Osteitis and Superinfection, *Am. J. Syph. & Neurol.* **19**:339, 1935.

11. Newman, B. A., and Saunders, H. C.: Skeletal System Manifestations During Secondary Syphilis, *New York State J. Med.* **38**:788, 1938.

12. Farina, A.: Su un caso di osteomielite gummosa nel periodo precoce della lue, *Gior. di med. mil.* **87**:59, 1939.

13. Squires, J. B., and Weiner, A. L.: Osteitis in Early Syphilis: Report of a Case, *Arch. Dermat. & Syph.* **39**:830 (May) 1939.

14. Wile, U. J., and Welton, D. G.: Early Syphilitic Osteomyelitis with a Report of Two Cases, *Am. J. Syph., Gonorr. & Ven. Dis.* **24**:1, 1940.

The average age of the patients in both series was 27.9 years, a figure slightly higher than the age incidence for early syphilis in general.<sup>15</sup> Sex was not a factor in predisposing the patient to early osseous involvement, for the number of males and females was equal. In 11 of our 15 cases the condition occurred in Negroes, a ratio in keeping with the race distribution of our general clinic population.<sup>16</sup>

The bones of the skull are most frequently affected, the frontal, the parietal and the nasopalatine bones seeming especially vulnerable. The sternoclavicular region ranks next in order of frequency. The long bones are more rarely involved, more often in the lower extremity than in the upper. It is usual for the overlying periosteum to be involved when an area of bone is diseased. Occasionally, osteitis occurs without palpable or roentgenographically visible periosteal reaction. Osteomyelitis is the least common lesion, although involvement of the medullary cavity may be difficult to ascertain.

Pain and localized tumefaction are the cardinal symptoms of destructive bone lesions, in many cases completely overshadowing the other manifestations of early syphilis. The pain varies markedly in intensity, its severity seemingly being dependent on the degree of associated periostitis, and is worse at night. It should be noted, however, that at times lesions may be completely asymptomatic and are discovered only when the finding of one lesion prompts the clinician to make roentgenographic study of other portions of the skeleton. Stokes and Garver,<sup>17</sup> in a tabulation of the symptoms of early constitutional syphilis, have called attention to the frequency of the complaint of headache, which they noted in 24 per cent of their patients. Localized headache is an important symptom of destructive osseous lesions which involve the skull and is at times so severe that the possibility of acute syphilitic meningitis must be excluded. Tumefaction, indicative of concomitant periosteal involvement, is in no way different from that which occurs when periostitis alone is present. Tenderness, with little or no red-dening or local production of heat, is the rule. In rare instances localized areas of bone depression may be noted.

The onset of symptoms may precede or follow the secondary eruption. In 4 of our cases osseous involvement was evident before the rash appeared. In 2 others (cases 10 and 15) secondary manifesta-

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15. Padget, P.: Long Term Results in the Treatment of Early Syphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **34**:692, 1940.

16. Turner, T. B.: The Race and Sex Distribution of the Lesions of Syphilis in Ten Thousand Cases, *Bull. Johns Hopkins Hosp.* **46**:159, 1930.

17. Stokes, J. H., and Garver, V. C.: *Modern Clinical Syphilology*, ed. 2, Philadelphia, W. B. Saunders Company, 1936, p. 686.

tions were absent. Interestingly enough, in both of these cases the patients received treatment during the primary stage and in both extensive necrosis of the nasopalatine bones developed. The nature of the lesions in these 2 cases indicates that severe osseous relapse may complicate the treatment of early syphilis. That osseous lesions may appear after considerable antisyphilitic treatment has been recorded previously by Nitchew, Farina and Burrows.

The type of secondary eruption cannot be correlated with the extensiveness of the bone changes. Macular and maculopapular eruptions predominated in our series. No rupial or ecthymatous syphilides were noted.

The most frequently associated condition is arthritis, usually involving several joints, which responds rapidly to antisyphilitic treatment. We have noted involvement of the central nervous system only once. More often than not, a marked constitutional reaction is absent. Occasionally, as in our cases 10 and 15, and in those reported by other authors,<sup>18</sup> the patient is markedly ill, with fever, anemia, weakness, loss of weight and other evidences of toxemia.

The response to treatment is favorable. A Herxheimer reaction may follow the initial injection of an arsenical, but the pain is promptly relieved and associated periosteal reactions subside rapidly. In only 2 of our cases could the condition be described as malignant or treatment resistant. In these 2 remarkable cases (10 and 15) heroic measures were required to effect a cure.

In the usual course of events, the bone lesions heal promptly, leaving no residual evidence of their existence; serologic tests are reversed as promptly as in cases of uncomplicated early syphilis, and no late sequelae become manifest.

We have noted no instances of pathologic fracture resulting from early syphilitic osteitis. Saraceni<sup>19</sup> has recorded such an accident. In the case reported by Gougerot, Mathieu and Jais,<sup>8</sup> fracture occurred at the inner third of the clavicle, a common site of involvement. The interpretation of the case reported by Burrows<sup>20</sup> may be questioned, since the fracture, together with diffuse osteolytic lesions, occurred after serologic reversal and all lesions healed spontaneously, without further antisyphilitic treatment.

None of our patients acquired syphilis by blood transfusion. That severe osteomyelitis may dominate the picture of syphilis acquired in

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18. Newman and Saunders.<sup>11</sup> Farina.<sup>12</sup> Squires and Weiner.<sup>13</sup>

19. Saraceni, G.: Febbre, frattura spontanea e pigmentazione sifilitica, *Gazz. med. di Roma* **35**:421, 1909.

20. Burrows, H. J.: Pathological Fracture of the Humerus Complicating Late Secondary Syphilis, *Brit. J. Surg.* **24**:452, 1937.

this manner has been demonstrated by Mandelbaum and Saperstein<sup>21</sup> and by Pian and Frazier.<sup>22</sup>

#### PATHOLOGIC ASPECTS

Syphilis long has been known as "the great bone former," and certainly osteoplastic features are outstanding in the bone lesions of late syphilis. In the early stages of the disease, however, the fundamental process is one of osteolysis, with replacement by syphilitic granulation tissue.

Biopsy reports are included in the articles by Tauber and Goldman<sup>10</sup> and Wile and Welton,<sup>14</sup> and to these now may be added two

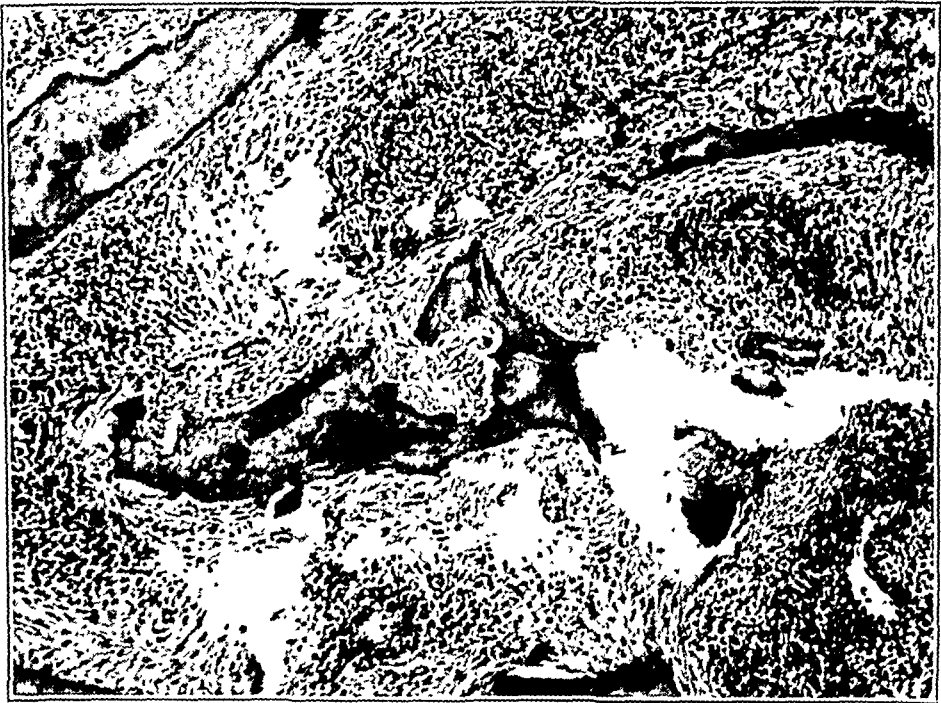


Fig. 1 (case 15).—Photomicrograph of nasal tissue taken for biopsy. Destruction of the bone is apparent, with round cell infiltration most marked around the blood vessels;  $\times 100$ .

from the present series. One autopsy report, that of Lancereaux, is available. Necrosis of bone with ingrowth of round cells is the feature common to all these reports.

21. Mandelbaum, H., and Saperstein, A. N.: Transmission of Syphilis by Blood Transfusion: A Case of Acute Gummatous Osteomyelitis, *J. A. M. A.* **106**:1061 (March 28) 1936.

22. Pian, H. C., and Frazier, C. N.: Transfusion Syphilis with Widespread Osteomyelitis and Cutaneous Lesions of an Erythema Multiforme Type, *Chinese M. J.* **57**:301, 1940.



Fig. 2 (case 8).—A moth-eaten area of destruction is visible in the frontal bone.

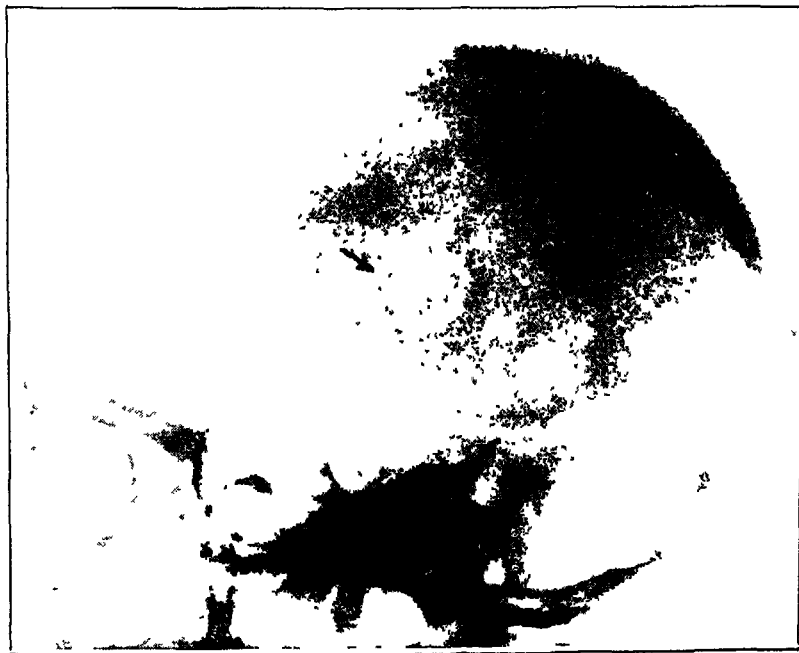


Fig. 3 (case 12).—A circumscribed area of destruction is apparent in the parietal bone.

## ROENTGENOLOGIC ASPECTS

In roentgenograms the lesions of the skull are characteristic, consisting of irregularly circular areas of decreased density having a moth-eaten appearance. The thinner and more porous bones of the calvarium are the ones commonly affected, and lesions are rare posterior to the lambdoidal suture. Elsewhere, the bony changes are less diagnostic, although involvement about the sternoclavicular joint is suggestive.

Swelling of soft tissue or wavy periosteal markings parallel to the surface of the bone are indicative of concomitant periostitis. The presence of medullary involvement can be inferred when the osteolytic process is noted to involve the inner portion of the cortex or (rarely) when sequestration can be detected as healing progresses.

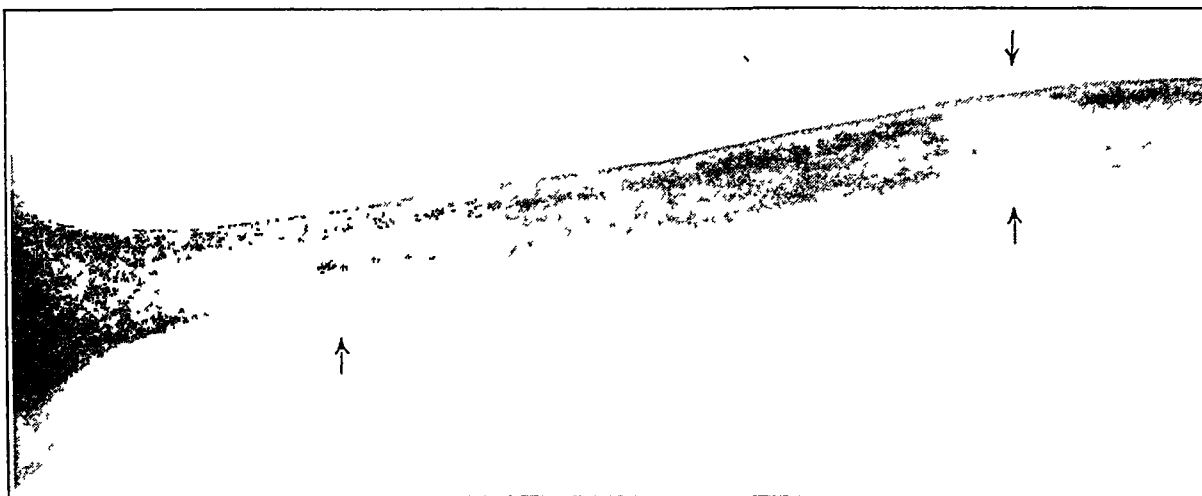


Fig. 4 (case 2).—Spotty areas of osteolysis are visible in the shaft of the humerus.

Early osseous syphilis must be differentiated most frequently from pyogenic osteomyelitis, tuberculous osteitis and multiple myeloma. Osteitis fibrosa cystica, Hodgkin's disease, leukemic infiltrations, actinomycosis, blastomycosis, coccidioidal granuloma, post-traumatic fibrous osteitis, xanthomatosis, neurofibromatosis and metastases of osteolytic carcinoma more rarely enter into the differential diagnosis.

Discussions of the roentgenographic features of early skeletal syphilis are available in the writings of Stewart<sup>23</sup> and Pancoast, Pendergrass and Schaeffer.<sup>24</sup>

23. Stewart, D. M.: Roentgenological Manifestations of Bone Syphilis, *Am. J. Roentgenol.* **40**:215, 1938.

24. Pancoast, H. K.; Pendergrass, E. P., and Schaeffer, J. P.: *The Head and Neck in Roentgen Diagnosis*, Springfield, Ill., Charles C. Thomas, Publisher, 1940, pp. 177-180.



## SUMMARY AND CONCLUSIONS

Destructive osseous lesions (osteitis, osteoperiostitis and osteomyelitis) may occur during the early period of syphilis. Fifteen cases from this clinic are presented and, with 15 others gathered from the literature, are analyzed.

The bones of the skull (frontal, parietal and nasopalatine) are most often involved. The sternoclavicular region is not infrequently affected. The long bones are more rarely attacked.

Destruction of the deeper skeletal structures may precede or follow the secondary eruption or may occur as the only manifestation of relapsing early syphilis.

The prompt response to appropriate therapy and the ultimately favorable serologic and clinical outcome indicate that involvement of the deeper skeletal structures adds little to the gravity of early syphilis, with a few notable exceptions.

The pathologic and roentgenographic features of the condition are discussed.

## REPORT OF ILLUSTRATIVE CASES

CASE 6.—H. W., an obese Negress aged 21, was admitted to the Syphilis Division on Oct. 6, 1928, complaining of severe headaches of one month's duration. These headaches were continuous but worse at night, so that she was kept awake. Most of the pain was referred to the frontal and left parietal regions.

She appeared well developed and well nourished. There were several annular, scaly, pea-sized papules on the upper lip and typical condylomata lata on the external genitalia. No local tenderness or bony irregularity was noted over the skull. The remainder of the physical examination revealed nothing abnormal.

Serologic tests for syphilis were strongly positive. A roentgenogram of the skull showed circumscribed areas of osteitis in the left frontal bone. The spinal fluid was normal.

Antisymphilitic treatment resulted in prompt symptomatic relief. The patient received ten injections of neoarsphenamine (0.7 Gm. each) and six injections of bismuth subsalicylate (0.2 Gm. each), after which she became delinquent. Serologic tests for syphilis became negative after six injections of neoarsphenamine and remained negative.

A follow-up examination was made Feb. 2, 1935. She had continued to feel well, and the physical examination revealed no evidence of syphilis. Serologic tests for syphilis were negative. Another roentgenogram of the skull showed an area of increased density in the left frontal bone, with a small area of rarefaction in the center, compatible with a diagnosis of healed osteitis.

CASE 12.—R. S., a Negress aged 22, was admitted to the General Medical Clinic on Oct. 16, 1935, complaining of pains in the head and chest. One month previously she had struck her head against a door, but had experienced no persistent pain until one week before admission. Examination at this time revealed a firm, rounded, slightly tender tumefaction over the right temporal bone. There was also tenderness over the right frontal bone and over the body of the sternum. Pain in the right temporomandibular joint resulted when the jaws were clenched. The genitalia, skin and mucous membranes were normal. A roentgenogram showed

moth-eaten areas of bone destruction, without evidence of new bone formation, in the right frontal and temporal bones. Serologic tests for syphilis were positive.

The patient returned six weeks later, complaining not only of cephalalgia but of a severe sore throat and a cutaneous rash, both of two weeks' duration. She was referred to the Syphilis Division, where physical examination showed a diffuse scaly maculopapular eruption over the trunk, an injected pharynx and four moist, flat-topped papules on the labia, material from which was positive for *Spirochaeta pallida* on dark field examination. She did not appear acutely ill or malnourished. The skeletal abnormalities previously noted were unchanged. The remainder of the physical examination revealed nothing abnormal.

Treatment with arsphenamine was started immediately. After four injections symptomatic relief was complete, but jaundice developed as a result of administration of the drug. Two months later treatment was resumed with neoarsphenamine, and in the following eighteen months she received thirty-one injections of neoarsphenamine (0.6 Gm. each) and twenty-eight injections of bismuth subsalicylate (0.2 Gm. each). Reversal of the serologic reactions was achieved within five months and was maintained. A roentgenogram taken Aug. 19, 1936 showed complete healing of the bone lesions. The spinal fluid examined on August 26 was negative for *S. pallida*. Complete physical examination on Aug. 4, 1938 revealed no clinical evidence of syphilis.

CASE 15.—F. L., a white salesman aged 27, noticed the development of a penile lesion in July 1939. Dark field examination was not done, but serologic tests for syphilis were negative. On clinical grounds alone antisyphilitic treatment was started elsewhere and 12 intravenous injections given, together with inunctions of mercury. Despite this treatment, the penile lesion did not heal, and the patient was hospitalized in Atlanta, Ga. Here a 3 plus Wassermann reaction of the blood was reported. Under further antisyphilitic treatment and local applications the lesion slowly healed.

After eight months of regular antisyphilitic treatment, and during a course of bismuth therapy, a painful nodular swelling developed on the hard palate, which gradually progressed, eventually destroying the palate.

He was admitted to the Johns Hopkins Hospital on June 18, 1940. At this time, he appeared seriously ill and grossly undernourished. There was diffuse, patchy alopecia. The central portion of the hard palate was destroyed over an area 6 cm. in diameter. The nasal bones above the palate were destroyed, and it was possible to look upward as far as the base of the skull. One centimeter behind the glans penis was an indurated scar encircling the shaft. The remainder of the examination revealed nothing abnormal.

The results of flocculation tests for syphilis were positive, and there was 80 to 90 units of reagin in the blood as determined by quantitative titration. A roentgenogram showed destruction of the bones of the face, particularly in the region of the hard palate. The calvarium was normal. The spinal fluid was negative for organisms. A biopsy specimen was removed from the nose. Microscopic study showed ulceration of the stratified squamous epithelium, areas of bone destruction and heavy infiltration of mononuclear inflammatory cells, especially about the blood vessels.

The patient was inoculated with tertian malaria and had a course of twelve satisfactory paroxysms, with a temperature of 105 F. or over. During the course of the malaria, however, the lesion in the nasopharynx did not heal but expanded to involve more of the palate and the maxilla.

In an effort to control the situation, the patient was given massive arsenical treatment with mapharsen. He received 90 mg. of the drug in three divided doses the first day and 160 mg. a day in four doses for the next three days. Simultaneously he was given 15 Gm. of potassium iodide per day, but the latter medication was discontinued when pustular iododerma developed. Sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) powder was applied locally to the nasopharynx to prevent secondary infection.

This intensive treatment resulted in relief of pain and dramatically prompt healing of the nasal lesion. The patient was fitted with a dental prosthesis and advised to continue regular antisyphilitic treatment. Since then he has received alternate courses of mapharsen and a bismuth compound in the usual therapeutic doses and has remained well.

# Progress in Internal Medicine

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## DISEASES OF NUTRITION

REVIEW OF CERTAIN RECENT CONTRIBUTIONS

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Advances in the field of nutrition in the past have been of interest only to a limited few. Since the recent national emergency, however, advances in this field have become of great importance to every one. The potential necessity of limitation of buying power makes it now important that every one be acquainted with what and how much food constitutes a well balanced diet. A national campaign to inform the public in this direction already has begun.

Studies of vitamins and other essential nutrient substances during the past year have been most actively conducted. The general recognition and acceptance of the conception that deficiency of vitamins usually is multiple rather than single is encouraging. The close relation between the liver and metabolism of vitamins again has been emphasized, and important advances in this direction have been accomplished.

### VITAMIN A

*Chemical and Physiologic Properties.*—During 1941 there has been an unusually large number of extensive physiologic studies on vitamin A. Some of the most interesting have been those concerned with the effects of vitamin A on the skeletal system of animals. In the 1940 review of nutrition<sup>1</sup> the work of several authors was reported in which it was found that after certain animals subsisted on diets deficient in vitamin A widespread degeneration of the central and peripheral nervous systems developed. It was suggested that these changes were due directly to the

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From the Division of Medicine (Dr. Butt and Dr. Wilder), the Mayo Clinic.

1. Butt, H. R., and Leary, W. V.: Diseases of Nutrition: Review of Certain Recent Contributions, Arch. Int. Med. **67**:411-465 (Feb.) 1941.

destructive effects of vitamin A deficiency on the nervous system. Recent papers by Mellanby<sup>2</sup> and Wolbach and Bessey,<sup>3</sup> however, bring out the inference that one of the main functions of vitamin A is to influence the structure of growing bone. It is stressed that this function is accomplished, perhaps, by limitation of the number and the degree of activity of osteoblasts and osteoclasts. Mellanby has shown that in the growing dog osteoblastic and osteoclastic activity is increased, with resulting proliferation of cancellous bone at the expense of compact bone. Thus, many bones lose their normally fine molding and outlines and become somewhat thickened and enlarged; some of the main zones where such overgrowth of bone occurs are in the skull and the vertebral column. Apparently, these overgrowths of bone are related to degenerative changes in the brain and in cranial and peripheral nerves. The bony overgrowth and the degenerative changes in nerves are greatest in the cervical region of the spinal cord, but the anterior and posterior root ganglions of the spinal cord also may be compressed and the nerve fibers destroyed by overgrowth of the vertebral bone. This evidence suggests that changes in the nervous system which formerly were thought to be the direct results of deficiency of vitamin A actually were results of overgrowth of bone in the vicinity of the affected nerves and nerve cells and of pressure effects resulting therefrom. It has also been demonstrated that in cattle fed rations deficient in vitamin A there develops an increase in the pressure of the cerebrospinal fluid. This also is said to be a result of bony overgrowth and pressure on the ventricles.<sup>4</sup> Organic changes resulting from bony overgrowth in the ear also have been reported.<sup>5</sup> The necessity of vitamin A in the normal growth of teeth also has been stressed in two extensive studies.<sup>6</sup>

In recent investigations the role of the liver in the storage of vitamin A continues to be emphasized. In a study by Ralli and her asso-

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2. Mellanby, E.: Skeletal Changes Affecting the Nervous System Produced in Young Dogs by Diets Deficient in Vitamin A, *J. Physiol.* **99**:467-486 (June 30) 1941.

3. Wolbach, S. B., and Bessey, O. A.: Vitamin A Deficiency and the Central Nervous System, *Am. J. Path.* **17**:586 (July) 1941.

4. Moore, L. A., and Sykes, J. F.: Terminal Cerebrospinal Fluid Pressure Values in Vitamin A Deficiency, *Am. J. Physiol.* **134**:436-439 (Sept.) 1941.

5. Perlman, H. B., and Willard, J.: The Ear in Experimental Vitamin A Deficiency, *Ann. Otol., Rhin. & Laryng.* **50**:349-362 (June) 1941.

6. Burn, C. G.; Orten, A. U., and Smith, A. H.: Changes in the Structure of the Developing Tooth in Rats Maintained on a Diet Deficient in Vitamin A, *Yale J. Biol. & Med.* **13**:817-830 (July) 1941. Schour, I.; Hoffman, M. M., and Smith, M. C.: Changes in the Incisor Teeth of Albino Rats with Vitamin A Deficiency and the Effects of Replacement Therapy, *Am. J. Path.* **17**:529-562 (July) 1941.

ciates<sup>7</sup> specimens of the livers of 25 healthy persons killed in accidents and 91 other subjects who had suffered from various diseases were obtained at necropsy, in most cases within twenty-four hours after death. These authors accepted the hypothesis that the normal liver contains at least 40,000 U. S. P. units of vitamin A per hundred grams of hepatic tissue. If this content is accepted as constituting a normal value, then it is seen that there is a striking reduction in the concentration of vitamin A in the livers of patients who have cirrhosis or acute infection. Also, on the basis of study of material obtained at necropsy, Ahmad and Seshan<sup>8</sup> reported that the average reserve of vitamin A in the liver in persons of the working class in India is between 7 and 10 micrograms per gram of hepatic tissue.

The particular site of storage of vitamin A in the liver has always been debatable. Cox<sup>9</sup> suggested that vitamin A is stored in the Kupffer cells. Other zones of storage have been suggested by Popper and his associates.<sup>10</sup>

That the liver is intimately connected with vitamin A metabolism cannot be denied. Horton and his co-workers<sup>11</sup> have shown that when vitamin A was not included in the diet of rats the concentration of the vitamin in the blood and the liver declined in seeming ratio to the deficiency. They pointed out that a normal concentration of the vitamin in the blood cannot be maintained unless there is adequate storage of it in the liver and that therefore as the liver stores are depleted the concentration in the blood gradually decreases. Complete absence of vitamin A occurs at about the same time in the blood and in the liver. A conception of the manner in which vitamin A is mobilized from its reserves is provided by the work of Young and Wald.<sup>12</sup> These authors

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7. Ralli, E. P.; Papper, E.; Paley, K., and Bauman, E.: Vitamin A and Carotene Content of Human Liver in Normal and in Diseased Subjects: An Analysis of One Hundred and Sixteen Human Livers, *Arch. Int. Med.* **68**:102-111 (July) 1941.

8. Ahmad, B., and Seshan, P. K.: Vitamin A and Carotene Reserves in Human Livers, *Indian M. Gaz.* **76**:156-157 (March) 1941.

9. Cox, A. J.: Site of Vitamin A Storage in the Liver, *Proc. Soc. Exper. Biol. & Med.* **47**:333-335 (June) 1941.

10. Popper, H., and Greenberg, R.: Visualization of Vitamin A in Rat Organs by Fluorescence Microscopy, *Arch. Path.* **32**:11-32 (July) 1941. Popper, H., and Ragins, A. B.: Histologic Demonstration of Vitamin A in Tumors, *ibid.* **32**:258-271 (Aug.) 1941. Popper, H.: Histologic Distribution of Vitamin A in Human Organs Under Normal and Under Pathologic Conditions, *ibid.* **31**:766-802 (June) 1941.

11. Horton, P. B.; Murrill, W. A., and Curtis, A. C.: Vitamin A and Carotene: I. The Determination of Vitamin A in the Blood and Liver as an Index of Vitamin A Nutrition of the Rat, *J. Clin. Investigation* **20**:387-393 (July) 1941.

12. Young, G., and Wald, G.: The Mobilization of Vitamin A by the Sympathico-Adrenal System, *Am. J. Physiol.* **131**:210-215 (Nov.) 1940.

observed that excision of a lobe of the liver in the rabbit results in decreases of about 25 per cent in the vitamin A content and 50 per cent in the carotene content of the remaining part of the organ. At the same time that the lobe of liver is removed, the value for vitamin A in the blood increases to three to seven and a half times the original value. It was also observed that electric stimulation of the splanchnic nerve results in a large increase of vitamin A in the blood and that the intravenous injection of epinephrine causes a similar increase. The authors concluded, therefore, that vitamin A is mobilized from its reserves in the liver by sympathetic-adrenal stimulation, comparable to that which mobilizes sugar and certain plasma proteins.

Again, it has been shown by Sherman<sup>13</sup> that the unsaturated fatty acids interfere with some phase of the metabolism of carotene and of vitamin A. It has been reported<sup>14</sup> that although carotene and xanthophyll are somewhat readily excreted in human feces, it appears that vitamin A is not excreted until the intake reaches a threshold value considerably more than all ordinary dietary levels and that when this threshold value is exceeded the fraction excreted increases with the intake.

*Methods of Measuring Vitamin A Deficiency.*—Much controversy and confusion continue to be associated with this subject. For physical methods of measuring vitamin A, the reader is referred to several recent reports.<sup>15</sup> Some workers<sup>16</sup> contended that the adaptation to dark test as an index of vitamin A deficiency is inadequate, whereas others<sup>17</sup> expressed the belief that the continued use of the biophotometer in the

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13. Sherman, W. C.: The Effect of Certain Fats and Unsaturated Fatty Acids upon the Utilization of Carotene, *J. Nutrition* **22**:153-165 (Aug.) 1941.

14. Wald, G.; Carroll, W. R., and Sciarra, D.: The Human Excretion of Carotenoids and Vitamin A, *Science* **94**:95-96 (July 25) 1941.

15. Mattill, H. H.: Fat-Soluble Vitamins, in Luck, J. M., and Smith, J. H. C.: *Annual Review of Biochemistry*, Stanford University, Calif., Stanford University Press, 1941, vol. 10, pp. 395-422. Wilkie, J. B.: Physical and Chemical Determination of Vitamin A, *Indust. & Engin. Chem. (Analyt. Ed.)* **13**:209-211 (April 15) 1941. Peterson, W. J.: Recent Developments in Methods for Determining Carotene, *ibid.* **13**:212-216 (April 15) 1941. Parker, A. E., and Oser, B. L.: Photoelectric Photometer for Vitamin A Estimation, *ibid.* **13**:260-262 (April 15) 1941.

16. Dann, W. J., and Yarbrough, M. E.: Dark Adaptometer Readings of Subjects on a Diet Deficient in Vitamin A, *Arch. Ophth.* **25**:833-838 (May) 1941. Stewart, C. P.: Nutritional Factors in Dark Adaptation, *Edinburgh M. J.* **48**:217-237 (April) 1941.

17. (a) Eckardt, R. E., and Johnson, L. V.: A Comparison of Two Methods of Measuring Dark Adaptation, *J. Pediat.* **18**:195-199 (Feb.) 1941. (b) Jeans, P. C.; Blanchard, E. L., and Satterthwaite, F. E.: Dark Adaptation and Vitamin A: Further Studies with the Biophotometer, *ibid.* **18**:170-194 (Feb.) 1941.

study of vitamin A deficiency is valid. The recent extensive work of Jeans and his associates<sup>17b</sup> would tend to show that the biophotometer gives rather constant results concerning the status of vitamin A among human beings. Jeans has pointed out that the apparently inconsistent results obtained with his technic by other authors have a logical explanation in the variability of the status of the subjects rather than in the fallibility of the test itself. Subjects in good health with an ample intake of vitamin A react normally to the test at all times. It was observed that the most frequent and usual cause of impaired adaptation seemed to be deficiency in utilization resulting from illness, especially from illness due to infection. Jeans and associates also observed that there was a seasonal incidence of dysadaptation: The greater incidence was found to obtain in the winter; the lesser, in the summer. The authors expressed the belief that seasonal incidence probably is more closely related to infection than to seasonal variations in diet.

Definite correlation between the results of biophotometric tests and the vitamin A content of human blood has not yet been established.<sup>18</sup> In an excellent and extensive study, Josephs and his associates<sup>18b</sup> asked a pertinent question: "What is meant by vitamin A deficiency?" They pointed out that deficiency of vitamin A may be defined as "the state that is reached when the reserves are so reduced that they are unable any longer to prevent changes characteristic of deficiency" or "a state in which the distribution is so interfered with that the tissues are no longer supplied with sufficient vitamin to prevent characteristic changes." They reemphasized that knowledge of the level of vitamin A in the blood is of no value unless it is possible to learn the significance of the level in relation to storage and adequate distribution of the vitamin. The content of vitamin A in the blood has no constant relation to the store of the vitamin. The only conclusion Josephs and his associates reached was that a high value for vitamin A in the blood is inconsistent with deficiency of the vitamin. Although they expressed the belief that adaptation to dark time is definitely related to a poor diet and low content of vitamin A in the blood, yet moderate prolongation of the adaptation time has little diagnostic significance. Therefore, it cannot be said that such prolongation is presumptive evidence that deficiency exists or that moderate prolongation is evidence that mild deficiency exists. In this paper the whole question is dealt with fairly. It should be read by any one interested in the measurement of deficiency of vitamin A.

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18. (a) Caveness, H. L.; Satterfield, G. H., and Dann, W. J.: Correlation of the Results of the Biophotometer Test with Vitamin A Content of Human Blood, *Arch. Ophth.* **25**:827-832 (May) 1941. (b) Josephs, H. W.; Baber, M., and Conn, H.: Studies in Vitamin A.: Relation of Blood Level and Adaptation to Dim Light to Diet, *Bull. Johns Hopkins Hosp.* **68**:375-387 (May) 1941.



Kruse<sup>19</sup> suggested that biomicroscopy be employed in the detection of the early ocular changes resulting from vitamin A deficiency. He reported that of 143 persons in a low income group, 45 per cent had gross and 54 per cent had microscopic ocular lesions (xerosis conjunctivae) characteristic of avitaminosis A. The author suggested that xerosis probably precedes night blindness as an early sign of deficiency of vitamin A. Kruse recommended biomicroscopic examination as a simple, convenient objective method; when it is combined with gross examination all degrees of xerosis may be graded according to severity and extent. He suggested that this condition is relatively prevalent in the population at large. He also pointed out that the vascular reaction in the eyes of patients with vitamin A deficiency is distinct from that noted in the eyes of patients with ariboflavinosis.

*Role of Vitamin A in Health and Disease.*—Lathyrism is a disease caused by subsistence on a diet composed predominantly of a species of pea (*Lathyrus cicera*). The disease occurs during famine, especially in India and northern Africa, when the poorer classes of the population are reduced to subsistence on a diet composed largely of lathyrus peas. When the crop of wheat, barley and other cereals is poor, the ingestion of peas as the chief article of food for two or three months is sufficient to precipitate the disease in epidemic form. In a recent report from the department of medicine, Peiping Union Medical College, Peiping, China, Frazier and Tsao<sup>20</sup> stated that lathyrism is related to vitamin A deficiency rather than to the effects of a toxin contained in the legume. This disease is characterized clinically by the sudden onset of weakness of the legs, associated with difficulty in sitting or standing. There is gradually progressive spastic paralysis of the lower extremities, which gives the patient a hesitating, springy gait. The disease is not fatal, but if attacks recur it leaves the patient with muscular atrophy and contractures of the lower extremities. It was formerly thought that this disease was caused by a poisonous substance in the pea itself. Investigators have pointed out that where this disease occurred there was also a high incidence of night blindness and that the addition of eggs or meat to the diet prevented the appearance of the characteristic neurologic symptoms. Frazier and Tsao described a case of lathyrism in which the patient had the cutaneous lesions of vitamin A deficiency; with administration of halibut liver oil rapid and complete healing of the cutaneous lesions occurred, but

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19. Kruse, H. D.: Medical Evaluation of Nutritional Status: IV. The Ocular Manifestations of Avitaminosis A, with Especial Consideration of the Detection of Early Changes by Biomicroscopy, Pub. Health Rep. **56**:1301-1324 (June 27) 1941.

20. Frazier, C. M., and Tsao, S. M.: Association of Neuromuscular Symptoms and Cutaneous Lesions in Vitamin A Deficiency, Chinese M. J. **59**:399-415 (May) 1941.

muscular weakness did not abate. Even after fifty-two days of such treatment there was no appreciable return of strength.

Various ocular symptoms resulting from deficiency of vitamin A continue to be described. Sandels and her associates<sup>21</sup> have recently reported on a group of 119 children suffering from follicular conjunctivitis for whom supplementary treatment with vitamin A resulted in cure of the condition. It was pointed out that children who received 25,000 or 38,000 U. S. P. units of vitamin A daily did not recover any more rapidly than did those who received only 13,000 U. S. P. units daily. The authors suggested that a time factor apparently operates which limits the rate of healing of a lesion and that the intake of excessive doses of vitamin A does not increase this rate proportionately. The addition of vitamin D or milk to the diet had no effect on the rapidity of healing. A survey of the diets of these children revealed that in each instance the consumption of a diet which had a vitamin A content below 100 U. S. P. units per kilogram of body weight per day permitted the deficiency to develop, whereas a diet with a vitamin A content in excess of 100 to 160 U. S. P. units per kilogram of body weight per day protected a majority of the children against follicular conjunctivitis. It was suggested by the authors that when diets in which carotene furnishes a large proportion of the vitamin A value are utilized, the addition of 200 to 250 U. S. P. units of vitamin A per kilogram of body weight per day will provide a generous allowance for children between the ages of 6 and 12 years. It has been suggested,<sup>22</sup> further, that keratosis follicularis (Darier's disease) also is a result of deficiency of vitamin A. It is interesting to learn that ocular symptoms resulting from deficiency of vitamin A are not uncommon in Newfoundland and Labrador<sup>23</sup> and that they continue to be common in India.<sup>24</sup>

The importance of the liver in the metabolism of vitamin A has been observed in several clinical conditions. Xerophthalmia and keratomalacia associated with obstructive biliary cirrhosis have been reported.<sup>25</sup>

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21. Sandels, M. R.; Cate, H. D.; Wilkinson, K. P., and Graves, L. J.: Follicular Conjunctivitis in School Children as an Expression of Vitamin A Deficiency, *Am. J. Dis. Child.* **62**:101-114 (July) 1941.

22. Peck, S. M.; Chargin, L., and Sobotka, H.: Keratosis Follicularis (Darier's Disease): A Vitamin A Deficiency Disease, *Arch. Dermat. & Syph.* **43**:223-229 (Feb.) 1941.

23. Steven, D., and Wald, G.: Vitamin A Deficiency: A Field Study in Newfoundland and Labrador, *J. Nutrition* **21**:461-476 (May) 1941.

24. Kirwan, E. O'G.; Sen, K., and Biswas, R. B.: Nutrition and Its Bearing on Preventable Blindness and Eye Diseases in Bengal: Preliminary Report, *Indian J. M. Research* **29**:119-124 (Jan.) 1941.

25. Stone, J. B., and Courtney, R. H.: Xerophthalmia and Keratomalacia Associated with Obstructive Biliary Cirrhosis, *Virginia M. Monthly* **68**:159-163 (March) 1941.

Woodruff and Wright,<sup>26</sup> using a new photometric test, have demonstrated that a prolonged adaptation to dark time is present in cases of obstructive jaundice. They assumed that this is a result of deficient absorption of vitamin A. That deficiency of vitamin A may result from poor absorption of the vitamin also has been reported in cases of diarrhea<sup>27</sup> and celiac disease.<sup>28</sup> In an extensive report Nylung and With<sup>29</sup> emphasized that perhaps 95 to 100 per cent of the total content of vitamin A in the body is to be found in the liver. It is assumed that the vitamin A content of the liver, therefore, is an index of the saturation of the organism with the vitamin; on the basis of the experience of Nylung and With this assumption seems rather warranted, and it appears that it would be true both under normal and under pathologic conditions. The authors, however, were careful to point out, as have others, that a liver which has a low vitamin A reserve, or even a liver which lacks the vitamin, does not constitute proof that a clinical deficiency of vitamin A exists.

In other reports the effect of vitamin A on the secretion of gastric juice<sup>30</sup> and the use of vitamin A in the treatment of gastric ulcer<sup>31</sup> have been considered. Murrill and associates<sup>32</sup> found that among diabetic patients the average concentration of carotene in the blood was significantly higher than it was among nondiabetic persons, whereas the concentration of vitamin A in the blood remained the same as that of persons without diabetes. A good review of studies on vitamin A from the clinical standpoint has been given by Moore.<sup>33</sup>

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26. Woodruff, M. F. A., and Wright, R. D.: The Diagnosis, Incidence and Treatment of Avitaminosis A and D in Obstructive Jaundice, *Australian & New Zealand J. Surg.* **10**:135-145 (Oct.) 1940.

27. Goldberg, H. K., and Schlivek, K.: Necrosis of the Cornea Due to Vitamin A Deficiency: Report of a Case, *Arch. Opth.* **25**:122-127 (Jan.) 1941.

28. May, C. D., and McCreary, J. F.: The Absorption of Vitamin A in Celiac Disease: Interpretation of the Vitamin A Absorption Test, *J. Pediat.* **18**:200-209 (Feb.) 1941.

29. Nylung, C. E., and With, T. K.: On the Demonstration of Vitamin A Deficiency in Man, *Acta med. Scandinav.* **106**:202-228, 1941.

30. Földes, F., and Vajda, G.: Effect of Vitamin A on the Secretion of Gastric Juice in Deficient Hydrochloric Acid Production, *Brit. M. J.* **1**:317-318 (March 1) 1941.

31. Seelig, S. F.: Treatment of Gastric Ulcer with Vitamin A, *Guy's Hosp. Rep.* **90**:41-54, 1940-1941.

32. Murrill, W. A.; Horton, P. B.; Leiberman, E., and Newburgh, L. H.: Vitamin A and Carotene: II. Vitamin A and Carotene Metabolism in Diabetics and Normals, *J. Clin. Investigation* **20**:395-400 (July) 1941.

33. Moore, T.: Vitamin A, *Post-Grad. M. J.* **17**:52-60 (April) 1941.

## VITAMIN B COMPLEX

*Chemical and Physiologic Properties.*—This interesting complex has continued to receive considerable attention during the past year. Perhaps one of the most interesting studies in this particular field has been work which shows that some relation exists between the development of cancer and cirrhosis in animals and a deficiency of various members of this complex. It has been known for some time that when dimethylamino-azobenzene (butter yellow) is fed to rats subsisting on a diet of wild rice and carrots, cirrhosis and eventual cancer of the liver regularly occur. If the basal diet is supplemented, however, by liver or yeast, the liver of the animal is completely protected against the toxic effects of the chemical. These experiments, originally done by Nakahara and Kinosipa, have been amply confirmed recently by Rhoads<sup>34</sup> and his associates, who have also extended the experiments of the Japanese investigators. In their studies they found that the liver of rats after one hundred and fifty days of subsistence on a basal diet plus butter yellow was always the site of marked cirrhosis and primary cancer. The livers of rats subsisting on the same diets and the same amount of butter yellow, however, were entirely normal as long as 15 per cent of the diet was composed of a certain brand of yeast. It was found that although deficiency of riboflavin rendered the animals more susceptible to the two diseases, lack of this protective power of pure riboflavin suggested that some other deficiency also was present. Subsequently, these authors demonstrated that the ingestion of riboflavin mixed with casein substantially protected rats against cancer of the liver formerly produced by feeding them butter yellow. The authors expressed the belief that the results of these experiments provided proof that toxemia can, in fact, cause a deficiency disease by interfering with the function of the enzyme in which the vitamin acts. Others<sup>35</sup> have shown that spontaneous mammary carcinoma disappeared completely in 30 per cent of treated mice after the intravenous injection of a watery yeast extract. Their studies<sup>35c</sup> showed that pantothenic acid, riboflavin and thiamine alone have no or little effect on the growth of tumors and that yeast alone will

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34. Rhoads, C. P.: Physiological Aspects of Vitamin Deficiency, Proc. Inst. Med. Chicago **13**:198-205 (Nov. 15) 1940.

35. (a) Lewisohn, R.; Leuchtenberger, C.; Leuchtenberger, R., and Laszlo, D.: Effect of Intravenous Injections of Yeast Extract on Spontaneous Breast Carcinomas in Mice, Proc. Soc. Exper. Biol. & Med. **43**:558-561 (March) 1940; (b) The Treatment of Spontaneous Breast Adenocarcinomas in Mice with Extracts of Spleen or Yeast, Am. J. Path. **17**:251-260 (March) 1941. (c) Lewisohn, R.; Leuchtenberger, C.; Leuchtenberger, R.; Laszlo, D., and Bloch, K.: Prevention of Tumor Growth (Carcinoma 2163) by Intravenous Injections of Yeast and Vitamins, Science **94**:70-71 (July 18) 1941.

prevent the growth of tumors in only about 20 per cent of cases. However, the tumor-preventing effect of yeast was markedly strengthened by the addition of pantothenic acid or riboflavin to the yeast extract. Addition of thiamine to the extract did not improve the tumor-preventing action.

Cirrhosis of the liver in rats has been produced in a number of different ways. The inhalation of carbon tetrachloride and the ingestion of diets high in fat with large doses of alcohol or the use of diets containing selenium all have been capable of producing a cirrhotic picture in the liver of rats. Rich and Hamilton<sup>36</sup> revived these studies last year when they reported that cirrhosis of the liver could be produced in rabbits by dietary deficiency and could be prevented by the feeding of yeast. Some authors<sup>37</sup> have reported the development of cirrhosis among rats suffering from a dietary deficiency, which was reduced by the administration of choline. The feeding of cystine ameliorated the cirrhosis, but the daily administration of choline or yeast neutralized more or less completely the effects of cystine on the liver. Confirming a long-known clinical fact, Lillie and his associates<sup>38</sup> reported results of experiments which suggested that alcohol constitutes an additional insult to hepatic tissue already injured by dietary deficiency. The authors at the time at which they wrote could make no statement as to the nature of the deficiency or deficiencies in the diet used which permitted or caused the development of hepatic cirrhosis.

Using one of the diets described by Rich and Hamilton,<sup>36</sup> Machella and Maguire<sup>39</sup> were unable to confirm the report made by the first-named two authors. Histologic evidence of hepatic cirrhosis did not develop in their animals, in spite of the fact that the usual signs of deficiency of the vitamin B complex became apparent. The authors suggested that the cirrhotic process in the liver of rabbits noted by Rich and Hamilton might have been due to infection with coccidia.

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36. Rich, A. R., and Hamilton, J. D.: The Experimental Production of Cirrhosis of the Liver by Means of a Deficient Diet, *Bull. Johns Hopkins Hosp.* **66**:185-196 (March) 1940.

37. Earle, D. P., Jr., and Victor, J.: Cirrhosis of the Liver Caused by Excess Dietary Cystine, *J. Exper. Med.* **73**:161-172 (Feb.) 1941. György, P., and Goldblatt, H.: Experimental Production of Dietary Liver Injury (Necrosis, Cirrhosis) in Rats, *Proc. Soc. Exper. Biol. & Med.* **46**:492-494 (March) 1941.

38. Lillie, R. D.; Daft, F. S., and Sebrell, W. H., Jr.: Cirrhosis of the Liver in Rats on a Deficient Diet and the Effect of Alcohol, *Pub. Health Rep.* **56**:1255-1258 (June 13) 1941.

39. Machella, T. E., and Maguire, E. F.: An Attempt to Produce Hepatic Cirrhosis by a Diet Deficient in Vitamin B Complex, *Proc. Soc. Exper. Biol. & Med.* **46**:502-507 (March) 1941.

It seems fairly well established<sup>40</sup> that the vitamin B complex plays some role in the metabolism of fat, and most investigators<sup>41</sup> now agree that choline probably is a member of the vitamin B complex.

The relation of the vitamin B complex to the syndrome produced by adrenalectomy<sup>42</sup> and the interrelation between this complex and the anterior lobe of the pituitary body<sup>43</sup> also have received consideration. It has also been reported<sup>44</sup> that the effect of yeast on the increased motility of the gastrointestinal tract apparently is due to the presence of live yeast in the gastrointestinal tract itself.

*Methods of Measurement.*—Attempts to measure quantitatively the vitamin B complex have met with many difficulties. Recently, Golden<sup>45</sup> has described in some detail intestinal changes seen roentgenologically which he asserted are results of deficiency of the vitamin B complex. It has been observed that the intestines revert to normal after administration of the vitamin B complex. Although the author did not claim these lesions to be specific, he did express the belief that they prove helpful in the search for the cause and relief of obscure abdominal symptoms.

*Clinical Deficiencies.*—The role of the vitamin B complex in normal nutrition<sup>46</sup> and the syndrome of multiple deficiencies has been well discussed.<sup>47</sup> In an interesting paper Spies and his associates<sup>48</sup> reported

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40. Longenecker, H. E.; Gavin, G., and McHenry, E. W.: The Relation of the Vitamin B Complex and Liver and Pancreas Extracts to Fat Synthesis, *J. Biol. Chem.* **139**:611-620 (June) 1941. McHenry, E. W., and Gavin, G.: The B Vitamins and Fat Metabolism: IV. The Synthesis of Fat from Protein, *ibid.* **138**:471-475 (April) 1941. Richter, C. P., and Hawkes, C. D.: The Dependence of the Carbohydrate, Fat and Protein Appetite of Rats on the Various Components of the Vitamin B Complex, *Am. J. Physiol.* **131**:639-649 (Jan.) 1941.

41. György, P., and Goldblatt, H.: Choline as a Member of the Vitamin B<sub>2</sub> Complex, *J. Exper. Med.* **72**:1-10 (July) 1940. Griffith, W. H.: The Nutritional Importance of Choline, *J. Nutrition* **22**:239-253 (Sept.) 1941.

42. Clark, W. G.: Vitamin B Complex and Adrenalectomy, *Endocrinology* **28**:545-554 (April) 1941.

43. Sutton, D. C.: Interrelation Between the Vitamin B Complex and the Anterior Lobe of the Pituitary Gland, *South. M. J.* **34**:47-51 (Jan.) 1941.

44. Russell, R. A., and Nasset, E. S.: The Effects of Various Vitamin Supplements and of Whole Yeast on the Digestion and Absorption of the Carbohydrate of a Complete Diet, *J. Nutrition* **22**:287-294 (Sept.) 1941.

45. Golden, R.: The Small Intestine in Vitamin B Deficiency, *J. A. M. A.* **117**:913-917 (Sept. 13) 1941.

46. Elvehjem, C. A.: The Vitamin B Complex in Normal Nutrition, *Nature, London* **146**:669-672 (Nov. 23) 1940.

47. Sydenstricker, V. P.: The Syndrome of Multiple Vitamin Deficiency, *Ann. Int. Med.* **15**:45-51 (July) 1941. Sinclair, H. M.: The Vitamin B Complex, *Post-Grad. M. J.* **17**:3-12 (Jan.-Feb.) 1941. Jolliffe, N.: Recent Advances in Clinical Applications of the B-Vitamins, *J. Am. Dietet. A.* **17**:5-11 (Jan.) 1941.

48. Spies, T. D.; Grant, H. M., and Grant, J. M.: Observations on the Effectiveness of a Yeast-Peanut Butter Mixture in Vitamin B Complex Deficiencies: A Progress Report, *South. M. J.* **34**:159-161 (Feb.) 1941.

that a mixture containing 25 per cent yeast (dried brewers' yeast powder), 67 per cent peanut butter and 8 per cent peanut oil is an inexpensive and palatable food mixture useful for protection against pellagra, beriberi and ariboflavinosis. They found that 2 ounces (59 cc.) or more of this mixture administered daily as a supplement to the diet gradually improved the health of the persons who exhibited subclinical symptoms caused by a suboptimal intake of members of the vitamin B complex and that it retarded and prevented recurrence of these diseases among average malnourished persons living in an area in which deficiency diseases were endemic.

In a report of 21 cases of Wernicke's encephalopathy, Campbell and Russell<sup>49</sup> suggested that both thiamine and nicotinic acid be used in the treatment of this disease syndrome. It seemed likely that this syndrome is a multiple deficiency of constituents of the B complex.

In an excellent and extensive study, Patek and Post<sup>50</sup> reported that the administration of vitamin concentrates to patients who had cirrhosis of the liver provided a greater expectancy of life. Similar results have been obtained by other investigators.<sup>51</sup>

Recently, a syndrome was described by Lepore and Golden<sup>52</sup> which is claimed to be the result of deficiency of the vitamin B complex. Clinically, the syndrome is similar to that well known condition often called the "irritable bowel syndrome." In addition to this, the authors reported that a flat curve for tolerance to dextrose administered orally was obtained and that an abnormally small intestinal pattern was seen roentgenologically. These authors observed that clinical improvement often preceded improvement in the roentgenologic appearance of the small intestine but that within three to four weeks improvement in the small intestine usually was demonstrable. For the results obtained the amount of vitamin B complex administered seemed small. In a discussion of this paper, Sosman pointed out the necessity for hesitation in the matter of formulation of any large number of diagnoses of "vitamin B deficiency" until definite, accurate tests of what this complex really is are available.

Equivocal results have been reported after administration of the vitamin B complex to patients who have lichen planus,<sup>53</sup> acute anterior

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49. Campbell, A. C. P., and Russell, W. R.: Wernicke's Encephalopathy: The Clinical Features and Their Probable Relationship to Vitamin B Deficiency, *Quart. J. Med.* **10**:41-64 (Jan.) 1941.

50. Patek, A. J., Jr., and Post, J.: Treatment of Cirrhosis of the Liver by a Nutritious Diet and Supplements Rich in Vitamin B Complex, *J. Clin. Investigation* **20**:481-505 (Sept.) 1941.

51. Snell, A. M., and Butt, H. R.: Unpublished data.

52. Lepore, M. J., and Golden, R.: A Syndrome of Deficiency of the Vitamin B Complex, *J. A. M. A.* **117**:918-923 (Sept. 13) 1941.

53. Burgess, J. F.: The Treatment of Lichen Planus with Vitamin B Complex, *Canad. M. A. J.* **44**:120-123 (Feb.) 1941.

poliomyelitis<sup>54</sup> and various diseases of the eyes, ears, nose and throat.<sup>55</sup> A good review of this problem has been given recently by Jolliffe.<sup>56</sup>

#### THIAMINE (VITAMIN B<sub>1</sub>)

*Chemical and Physiologic Properties.*—The role of thiamine in carbohydrate metabolism, and particularly in pyruvate metabolism, continues to be actively studied. It has been shown<sup>57</sup> that after an injection of dextrose in a normal person the content of pyruvate in the blood is elevated and that this elevation reaches a maximum at the end of an hour and returns to the normal fasting range within three hours. It is observed that among those persons who have a deficiency of thiamine the fasting value for pyruvate in the blood is elevated and that the pyruvate curve after the ingestion of dextrose is abnormally elevated and prolonged. Others<sup>58</sup> have pointed out that twenty-nine to thirty-seven days on a thiamine-low diet is not long enough for a significant disturbance to occur in the intermediary carbohydrate metabolism of the normal young adult. These authors took the value for bisulfite-binding substances in the urine as a criterion.

Williams, Mason, Wilder and Smith<sup>59</sup> severely restricted the thiamine intake of 4 human subjects for eighty-eight days and observed, among other metabolic defects, an increase of the bisulfite-binding substances (which include pyruvic acid) in the blood when the subject was in the basal state and abnormally elevated and prolonged time curves for bisulfite-binding substances in the blood after the subject had exercised for three minutes.

Williams and Mason,<sup>60</sup> in a subsequent study of 11 persons whose intake of thiamine was restricted less severely but for a longer period,

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54. Helms, K.: Acute Anterior Poliomyelitis and Vitamin B Deficiency, *M. J. Australia* **1**:717-723 (June 14) 1941.

55. Veasey, C. A., Jr.: Vitamins of the B Group and Their Relation to Ophthalmology, *Tr. Am. Ophth. Soc.* **38**:538-579, 1940. Jones, I. H.: Vitamins and the Eye, Ear, Nose and Throat, *Laryngoscope* **51**:609-682 (July) 1941.

56. Jolliffe, N.: Newer Knowledge of the Vitamin B-Complex, *Bull. New York Acad. Med.* **17**:195-204 (March) 1941.

57. Bueding, E.; Stein, M. H., and Wortis, H.: Blood Pyruvate. Curves Following Glucose Ingestion in Normal and Thiamine-Deficient Subjects, *J. Biol. Chem.* **140**:697-703 (Sept.) 1941.

58. Shils, M. E.; Day, H. G., and McCollum, E. V.: The Urinary Excretion of Bisulfite Binding Substances by Human Adults on Thiamine-Low Diets, *Am. J. M. Sc.* **201**:561-569 (April) 1941.

59. Williams, R. D.; Mason, H. L.; Wilder, R. M., and Smith, B. F.: Observations on Induced Thiamine (Vitamin B<sub>1</sub>) Deficiency in Man, *Arch. Int. Med.* **66**:785-799 (Oct.) 1940.

60. Williams, R. D., and Mason, H. L.: Further Observations on Induced Thiamine (Vitamin B<sub>1</sub>) Deficiency and Thiamine Requirement of Man: Preliminary Report, *Proc. Staff Meet., Mayo Clin.* **16**:433-438 (July 9) 1941.



observed elevated values for blood pyruvic acid irregularly. In addition to disturbance of metabolism, the conspicuous manifestations of deficiency of thiamine were gross changes of behavior and other objective evidence of psychic disturbances involving mental depression, irritability and loss of efficiency.

Using a special method for micromasurement of pyruvic acid in the blood of rats, Li and Kato <sup>61</sup> reported that by the end of the first month of thiamine depletion the amount of pyruvate in the blood increased more than 260 per cent over normal basal amounts and that during the second month it increased almost 500 per cent. It was observed that the quantity of pyruvate in the blood appeared to correspond roughly to the severity of the clinical manifestations. On the injection of thiamine into these polyneuritic animals there was a marked decrease in the content of pyruvate in the blood. If after the injection of thiamine this characteristic decrease in blood pyruvate did not occur the animal died within twenty-four hours. In a similar study <sup>62</sup> it has been shown that there is a rapid increase in the bisulfite-binding substances in the urine of rats subsisting on a vitamin B<sub>1</sub>-deficient diet. The administration of thiamine brings the values for bisulfite-binding substances to normal within twenty-four hours. It is assumed that the rapid response to the administration of thiamine indicates that vitamin deficiency is responsible for the elevated values. It has also been pointed out <sup>63</sup> that the ingestion of a high fat diet will reduce the excretion of bisulfite-binding substances in the urine of rats deficient in thiamine.

Using a chemical method for measurement of the concentration of pyruvic acid in the blood, Kato and Li <sup>64</sup> reported that of a total of one hundred and fifty determinations made of the concentration of pyruvate in the blood of infants and children of all ages suffering from diverse diseases and conditions, the values in approximately 27 per cent were abnormally high, indicating that relative states of thiamine deficiency were present.

Apparently, a long-continued subminimal intake of thiamine hydrochloride produces a rather definite syndrome in dogs. Street and his

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61. Li, P. K., and Kato, K.: Determination of Blood Pyruvate in Vitamin B<sub>1</sub> Deficiency, *J. Lab. & Clin. Med.* **26**:1314-1321 (May) 1941.

62. Shils, M. E.; Day, H. G., and McCollum, E. V.: The Effect of Thiamine Deficiency in Rats on the Excretion of Pyruvic Acid and Bisulfite-Binding Substances in the Urine, *J. Biol. Chem.* **139**:145-161 (May) 1941.

63. Banerji, G. G.: Effect of a High-Fat Diet on the Excretion of Bisulphite-Binding Substances in the Urine of Rats Deficient in Vitamin B<sub>1</sub>, *Biochem. J.* **34**:1329-1333 (Sept.) 1940.

64. Kato, K., and Li, P. K.: Quantitative Determination of the Pyruvic Acid Content of the Blood in Infants and in Children: An Attempt to Diagnose Sub-clinical Deficiency of Vitamin B<sub>1</sub>, *Am. J. Dis. Child.* **61**:1222-1237 (June) 1941.

associates<sup>65</sup> studied dogs in which the store of thiamine had been depleted. These dogs were maintained in a state of subnutrition for seventy-six to two hundred and ninety-three days, receiving a diet containing thiamine only in amounts averaging about 2 micrograms per kilogram of body weight daily. In these animals there developed a condition characterized by moderate spasticity of the hindlegs, unsteadiness, staggering and vomiting. In 2 animals, after three hundred and forty-five and three hundred and fifty-four days, respectively, of this insufficient intake of thiamine, the administration of large doses of thiamine hydrochloride for a month failed to have an appreciable effect on the syndrome. Histologic studies of the nervous system of representative animals revealed extensive myelin degeneration both of the peripheral nerves and of the posterior column of the spinal cord. Other workers<sup>66</sup> have observed definite symptoms of cardiac failure among dogs subsisting on diets deficient in thiamine.

Since vitamins serve as catalysts in the various phases of cellular combustion, the requirements in intake of them undoubtedly vary as the combustion rate increases or decreases with changes in environmental temperature. An interesting but so far unconfirmed observation by Mills<sup>67</sup> was that the optimal requirements of thiamine per gram of food were twice as high at a temperature of 91 F. as they were at a temperature of 65 F. and that an intake of thiamine higher than that required for a temperature of 91 F. served to protect against the depressant effects of even more excessive heat. Mills observed that among young rats subsisting on a diet thoroughly adequate in every way except for thiamine content, signs of inadequacy (lowered consumption of food and retarded growth) developed in animals in the hot room at dietary thiamine values which were entirely adequate for animals in the cold room. Protection against the severe effects of excessive heat is afforded by an accessory intake of thiamine in excess of the ordinary daily need. Mills brought out the fact that the need for a higher content of thiamine in food in tropical warmth or in the summer heat of the temperate zone has certain important bearings on the problems of human existence. He stated that protein foods in general have a high content of thiamine, but that people tend to avoid them in the presence of tropical warmth because of their greater specific dynamic action and higher cost.

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65. Street, H. R.; Zimmerman, H. M.; Cowgill, G. R.; Hoff, H. E., and Fox, J. C., Jr.: Some Effects Produced by Long-Continued Subminimal Intakes of Vitamin B<sub>1</sub>, *Yale J. Biol. & Med.* **13**:293-308 (Jan.) 1941.

66. Swank, R. L.; Porter, R. R., and Yeomans, A.: The Production and Study of Cardiac Failure in Thiamine-Deficient Dogs, *Am. Heart J.* **22**:154-168 (Aug.) 1941.

67. Mills, C. A.: Environmental Temperatures and Thiamine Requirements, *Am. J. Physiol.* **133**:525-531 (July) 1941.

Drill,<sup>68</sup> in experimental studies on dogs, reported that anorexia is not a primary effect of hyperthyroidism in animals with this disease but is a secondary symptom referable to deficiency of thiamine. Many other interesting physiologic effects of thiamine also have been reported.<sup>69</sup>

*Methods of Measuring Vitamin B<sub>1</sub>.*—There continues to be considerable interest in this field. Several new methods for the measurement of thiamine in metabolic excretions, in the blood and in cereal products have been described.<sup>70</sup>

Cahill<sup>71</sup> reported that alterations of the fat-carbohydrate ratio of the diet of adult human beings have no significant effect on the urinary excretion of thiamine. He interpreted his observations to mean that in tests involving study of the excretion of thiamine in the urine no concern need be given to the fat-carbohydrate ratio of the foods eaten by the patients just prior to the time of determination.

Benson, Witzberger and Slobody<sup>72</sup> reported that the urinary excretion of thiamine among normal children ranges between 92 and 602 micrograms (of thiamine hydrochloride) per day and averages 268 micrograms per day. Their study was made on children between 7 and

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68. Drill, V. A.: The Calorie Intake and Weight Balance of Hyperthyroid Dogs in Relation to Vitamin B<sub>1</sub> and Yeast, *Am. J. Physiol.* **132**:629-635 (April) 1941.

69. Guerrant, M. V., and Dutcher, R. A.: The Influence of Exercise on the Growing Rat in the Presence and Absence of Vitamin B<sub>1</sub>, *J. Nutrition* **20**:589-598 (Dec.) 1940. Barnes, R. H., and MacKay, E. M.: Influence of Protamine Zinc Insulin upon Appetite During Anorexia of Vitamin B<sub>1</sub> Deficiency, *Proc. Soc. Exper. Biol. & Med.* **45**:759-762 (Dec.) 1940. Smith, A. H., and Meyer, C. E.: The Influence of Thiamine Deficiency on Citric Acid Excretion, *J. Biol. Chem.* **139**:227-231 (May) 1941. Govier, W. M., and Greer, C. M.: Studies on Shock Induced by Hemorrhage: I. Effect of Thiamine on Survival Time, *J. Pharmacol. & Exper. Therap.* **72**:317-320 (Aug.) 1941. Flexner, J.; Bruger, M., and Wright, I. S.: Experimental Atherosclerosis: II. Effect of Thiamine Hydrochloride and Ascorbic Acid on Experimental Atherosclerosis in Rabbits, *Arch. Path.* **31**:82-84 (Jan.) 1941.

70. Jowett, M.: The Estimation of Vitamin B<sub>1</sub> in Urine, *Biochem. J.* **34**:1348-1355 (Nov.) 1940. Slater, E. C.: The Thiochrome Method of Estimating Thiamine (Vitamin B<sub>1</sub>) in Urine, Milk and Cereal Products, *Australian J. Exper. Biol. & M. Sc.* **19**:29-32 (March) 1940. Schultz, A. S.; Atkin, L., and Frey, C. N.: A Method for the Determination of Thiamine and Certain of Its Metabolic Products in Urine, *J. Biol. Chem.* **136**:713-717 (Dec.) 1940. Hennessy, D. J.: Chemical Methods for the Determination of Vitamin B<sub>1</sub>, *Indust. & Engin. Chem. (Analyt. Ed.)* **13**:216-218 (April 15) 1941. Pollack, H.; Ellenberg, M., and Dolger, H.: Clinical Studies on Vitamin B<sub>1</sub> Excretion Determined by the Fermentation Method, *Arch. Int. Med.* **67**:793-804 (April) 1941.

71. Cahill, W. M.: Urinary Excretion of Thiamine on High Fat and High Carbohydrate Diets, *J. Nutrition* **21**:411-418 (April) 1941.

72. Benson, R. A.; Witzberger, M., and Slobody, L. B.: The Urinary Excretion of Thiamine in Normal Children, *J. Pediat.* **18**:617-620 (May) 1941.

10 years old. Using the method for measurement of thiamine described by Hennessy and Cerecedo, Najjar and Holt<sup>73</sup> found that the daily excretion of thiamine by 23 normal adult persons varied between the wide limits of 60 and 342 micrograms (of thiamine hydrochloride) a day. These observations are in agreement with those of many other workers. The authors found that the daily excretion of thiamine by children is comparable to that of adult persons, but a patient who had hyperthyroidism also had a low rate for excretion of thiamine, as was noted among other patients suffering from a definite vitamin B deficiency syndrome. The authors found that persons subsisting on a diet deficient in thiamine who are symptom free may excrete less thiamine than patients who have frank beriberi. Therefore they expressed the belief that if progress is to be made, it will be necessary to search for more sensitive tests, with results dependent on the immediate intake. It was also observed that their thiamine excretion test (intravenous injection of 1 mg. of thiamine hydrochloride and check of the urine for four hours thereafter) was a more reliable index of the bodily stores of thiamine than was the customary measurement of the total twenty-four hour output of thiamine in the urine, but it was difficult even by means of this excretion test to distinguish thiamine deficiency from thiamine subnutrition.

However, Williams and Mason,<sup>60</sup> who maintained human subjects on a constant diet for one hundred and forty days and gave thiamine hydrochloride in gradually increasing doses, found that the excretion of thiamine closely reflected the state of thiamine nutrition. The urinary excretion clearly distinguished between restriction of intake just prior to the test and prolonged, moderate restriction of this vitamin. The variations in the excretion of thiamine among so-called normal persons possibly represent, at least in part, variations in states of thiamine nutrition encountered in the population at large. In Najjar and Holt's<sup>73</sup> series, values for thiamine in the blood serum of several normal adult persons ranged, as a rule, between 1 and 3 micrograms (of thiamine hydrochloride) per hundred cubic centimeters. From some subjects they were unable to recover measurable quantities of thiamine. This led them to conclude that the value for thiamine in the serum alone does not constitute a satisfactory criterion for measurement of thiamine deficiency and that probably, like the value for the twenty-four hour excretion in the urine, it is dependent on the immediate intake of thiamine. Carden, Province and Ferrebee<sup>74</sup> also have pointed out that much more study is

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73. Najjar, V. A., and Holt, L. E.: Studies in Thiamine Excretion, *Bull. Johns Hopkins Hosp.* **67**:107-124 (Aug.) 1940.

74. Carden, G. A.; Province, W. D., and Ferrebee, J. W.: Clinical Experiences with the Measurement of the Urinary Excretion of Vitamin B<sub>1</sub>, *Proc. Soc. Exper. Biol. & Med.* **45**:1-5 (Oct.) 1940.

needed, for better understanding of the factors related to the saturation and urinary excretion of thiamine, before accurate interpretation of these results can be made. In one year these investigators were unable to find any patient whose urinary excretion of vitamin B<sub>1</sub> could not be increased to normal by the administration of small amounts of vitamins, amounts comparable to those obtained in an ordinary diet.

*Requirements of the Normal Person.*—Melnick, Robinson and Field <sup>75</sup> have shown that thiamine is stable during a sixteen hour incubation period at 37.5 C. in gastric juice with a  $p_H$  of 1.5 to 8 obtained from normal subjects. In the presence of an antacid, thiamine added to gastric juice may be absorbed or destroyed during this period of incubation. Thiamine was found to be stable in hemin-containing gastric juice and in gastric juice obtained from patients who had achlorhydria. On the other hand, when thiamine is incubated for sixteen hours with bile at its natural  $p_H$  there is an apparent loss of 50 to 90 per cent of the vitamin. As the reaction of the bile becomes acid, less thiamine is destroyed, and complete recovery can be obtained from samples incubated at a  $p_H$  of 4.5. Results obtained when thiamine is incubated with pancreatic juice are similar to those obtained when it is incubated with bile. It should be mentioned that all these experiments were conducted in vitro, an important factor, in that thiamine is more stable in its natural environment than it is in pure aqueous solution. The authors expressed the belief that the losses in vivo probably are appreciably less than those they noted in vitro, because of the protective action of the other constituents of the diet.

Stockholm, Althausen and Borson <sup>76</sup> recently reported that thiamine probably is absorbed in the intestine by means of simple diffusion and that absorption is roughly proportional to the concentration of thiamine in the intestine. These authors also concluded that phosphorylation did not play a dominant part in the rate of intestinal absorption of thiamine.

Little had been added to previous studies concerning the normal human requirements of thiamine before the report published recently by Williams and Mason.<sup>60</sup> These investigators found that 0.22 to 0.25 mg. of thiamine for each thousand calories of a mixed diet was not enough for 11 women, for in all of them signs and symptoms of deficiency developed when this amount of thiamine was provided. In a study of thiamine requirements they found that the optimal intake of thiamine for the subjects of their study was not less than 0.5 mg. and not more than 1.0 mg. per thousand calories obtained from a diet of ordinary composition.

75. Melnick, D.; Robinson, W. D., and Field, H., Jr.: Fate of Thiamine in the Digestive Secretions, *J. Biol. Chem.* **138**:49-61 (March) 1941.

76. Stockholm, M.; Althausen, T. L., and Borson, H. J.: Mechanism of Intestinal Absorption of Thiamine, *Proc. Soc. Exper. Biol. & Med.* **46**:387-390 (March) 1941.

Knott,<sup>77</sup> in a study of 12 infants 1 to 6 months old, substantiated previous conclusions, based on tests for urinary excretion, that 80 international units of thiamine daily represents the minimal requirements for infants in this age range. Other authors<sup>78</sup> observed that in the age group of 7 to 10 years 45 micrograms of thiamine per hundred calories, or 990 micrograms, daily seems to be adequate to maintain excellent health. The average amount of thiamine excreted by children of this age was found to be about 27 per cent of the intake.

In a study of a small number of healthy Javanese, Meyers<sup>79</sup> observed that the output of thiamine was considerably lower than the average found in the more temperate parts of the world. This author suggested the possibility that some sort of adaptation to a low intake of vitamin B<sub>1</sub> occurs among these persons. He pointed out that a low level of thiamine in the body stores should not without additional evidence be held to be associated directly with a deficiency syndrome. Undoubtedly, the intake of thiamine among the Javanese under consideration is much lower than the average intake in other parts of the world; it probably is, on the average, a level which might produce clinical symptoms among Caucasians under experimental conditions. Meyers' study suggested that a low intake of thiamine can continue for years without the production of gross clinical evidence of deficiency and that some degree of adaptation is possible.

Apparently there is a smaller amount of thiamine in evaporated milk than in whole milk.<sup>80</sup> Although 6 per cent of the thiamine in whole milk is present in a free state, the rest is combined in a nondialyzable form, probably being combined with protein.<sup>81</sup> Investigation of the effects of long cooking of cereals on the stability of thiamine<sup>82</sup> reveals that no significant loss occurs, whereas in the presence of alkali, such as in the cooking of baking powder muffins, the loss of thiamine may amount to as much as 50 per cent.<sup>83</sup>

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77. Knott, E. M.: Determination of Vitamin B<sub>1</sub> Requirement of Infants by Means of Urinary Excretion of Thiamine, *Proc. Soc. Exper. Biol. & Med.* **45**:765-766 (Dec.) 1940.

78. Benson, R. A.; Witzberger, C. M., and Slobody, L. B.: The Urinary Excretion of Thiamine in Normal Children, *J. Pediat.* **18**:617-620 (May) 1941.

79. Meyers, F. M.: Possible Adaptation to a Low Vitamin B<sub>1</sub> Intake, *Am. J. M. Sc.* **201**:785-789 (June) 1941.

80. Daniels, A. L.: Further Evidence of Destruction of Thiamine in Evaporated Milk, *Am. J. Dis. Child.* **62**:127-129 (July) 1941.

81. Halliday, N., and Deuel, H. J., Jr.: The Presence of Free and Combined Thiamine in Milk, *J. Biol. Chem.* **140**:555-561 (Aug.) 1941.

82. Hanning, F.: The Effect of Long Cooking upon the Stability of Thiamine (Vitamin B<sub>1</sub>) in Cereals, *J. Am. Dietet. A.* **17**:527-530 (June-July) 1941.

83. Fincke, M. L., and Little, R. R.: The Thiamine (Vitamin B<sub>1</sub>) Values of Wheat Germ Muffins, *J. Am. Dietet. A.* **17**:531-534 (June-July) 1941.

*Clinical Deficiencies of Thiamine.*—It seems fairly well established that a syndrome resembling neurasthenia can be produced by a diet deficient in thiamine. This problem is complicated by the fact that similar syndromes have been reported to be cured by nicotinic acid, pyridoxine and vitamin E. In an excellent discussion of this problem, Wortis and Jolliffe<sup>84</sup> reemphasized the fact that the clinical picture of this syndrome is extremely varied, that many similar pictures occur among apparently well nourished persons and that these symptoms frequently can be abated by psychotherapy as well as by vitamin therapy. Therefore, it should not be inferred that neurasthenia in every case is based on thiamine deficiency or other nutritional deficiencies, although it does seem fairly certain that a syndrome presenting many of the characteristics of the ill defined neurasthenic syndrome can be produced by nutritional deficiencies.

Investigation of the effect of thiamine in the treatment of various neurologic disturbances continues. The exact relation of thiamine to the metabolism of nerve tissue, however, is still incompletely understood.

Zillhardt, MacLean and Murphy<sup>85</sup> reported the results of a rather extensive study which suggest that the administration of thiamine hydrochloride may have a beneficial effect on those neural signs and symptoms of pernicious anemia that seem to be stationary in spite of persistent intensive anti-pernicious-anemia therapy. The authors pointed out that the beneficial effects occur during the first two months of treatment and that apparently the continued use of thiamine after this period does not produce any further changes. Again, the authors stressed the many variables involved in the attempt to quantitate neurologic symptoms and signs in such a clinical study.

Rapid relief of pain caused by herpes zoster of the trunk has been reported<sup>86</sup> to follow the intracutaneous and subcutaneous injection of 10 mg. of thiamine hydrochloride into a clear portion of skin between the anterior and the lateral patches of eruption. The effect was noted a few hours later, when the pain practically disappeared. To be of clinical value, this type of report requires a much larger series of cases than that which thus far has been reported.

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84. Wortis, H., and Jolliffe, N.: The Present Status of Vitamins in Nervous Health and Disease, *New York State J. Med.* **41**:1461-1470 (July 15) 1941.

85. Zillhardt, J. C.; MacLean, K., and Murphy, W. P.: The Effect of Thiamine on the Residual Neural Disturbances of Treated Pernicious Anemia, *Ann. Int. Med.* **15**:33-43 (July) 1941.

86. Smith, S. F.: Regional Injection of Thiamine Chloride in Herpes Zoster, *J. M. Soc. New Jersey* **38**:396-397 (Aug.) 1941.

In a well controlled study Rose and Jacobson<sup>87</sup> showed that thiamine hydrochloride has no specific beneficial effect in the treatment of trigeminal neuralgia.

In last year's review it was reported that among animals abstinence symptoms in addiction to morphine were markedly decreased after the administration of thiamine hydrochloride. In a well controlled study of morphine addiction in man, Himmelsbach<sup>88</sup> reported that the administration of thiamine prior to and after withdrawal of morphine had no demonstrable effect on the onset of the abstinence symptoms; likewise, the administration of thiamine during the course of addiction had no demonstrable effect on the patient. Similarly, it was stressed in last year's review that thiamine deficiency was the cause of delirium tremens. Wortis and Jolliffe<sup>84</sup> have not been able to confirm these observations. They did assert, however, that delirium tremens is a factor of considerable importance in the production of other nutritional disturbances of the nervous system (Wernicke's syndrome, deficiency of nicotinic acid, encephalopathy, peripheral neuropathy). For this reason, Wortis and Jolliffe expressed the belief that thiamine and nicotinic acid, as well as the entire vitamin B complex, should be administered to all patients who have delirium so that the development of peripheral neuropathy can be prevented. Wortis and Jolliffe<sup>84</sup> have reported clinical observations made in 27 cases of Wernicke's syndrome. They pointed out that this syndrome originally was described by Wernicke as probably constituting a combination of several nutritional deficiencies affecting the nervous system, one of which is deficiency of thiamine. Green, Carlson and Evans<sup>89</sup> recently have reported that a deficiency disease of foxes produced by the feeding of fish is analogous to Wernicke's disease in man. These authors assumed that this deficiency in foxes is a thiamine deficiency.

Considerable controversy continues to be apparent concerning the effect of thiamine hydrochloride on diabetes mellitus. It has been pointed out on several occasions that the administration of thiamine hydrochloride has no effect on the blood sugar of diabetic persons or on that of normal persons, nor does the intravenous injection of thiamine hydrochloride have any effect on the dextrose tolerance curve of diabetic and of non-

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87. Rose, A. S., and Jacobson, B. M.: Treatment of Trigeminal Neuralgia with Vitamin B<sub>1</sub> (Thiamine Hydrochloride), *Arch. Neurol. & Psychiat.* **44**:1307-1311 (Dec.) 1940.

88. Himmelsbach, C. K.: Thiamine in the Treatment of the Morphine Abstinence Syndrome in Man, *J. Pharmacol. & Exper. Therap.* **70**:293-296 (Nov.) 1940.

89. Green, R. G.; Carlson, W. E., and Evans, C. A.: A Deficiency Disease of Foxes Produced by Feeding Fish: B<sub>1</sub> Avitaminosis Analogous to Wernicke's Disease of Man, *J. Nutrition* **21**:243-256 (March) 1941.



diabetic persons.<sup>90</sup> In a study of 422 ambulant diabetic patients, Fein, Ralli and Jolliffe<sup>91</sup> observed that 9, or 2.1 per cent, had a symmetric type of peripheral neuropathy which was characteristic of peripheral neuropathy among persons having true vitamin B<sub>1</sub> deficiency. The daily oral administration of 10 mg. of thiamine hydrochloride without other changes in the regimen resulted in the cure of 8 subjects and improvement for the ninth. These authors concluded that the symmetric type of peripheral neuropathy, beginning first in, and involving primarily, the lower extremities of patients suffering from diabetes mellitus can be abated by the administration of thiamine hydrochloride. In their opinion, the condition is due to deficiency of vitamin B<sub>1</sub>. They, like others, reported inconsistent results in the treatment of single nerves or the vague aches and pains of diabetic patients.

Wallace<sup>92</sup> reported that the parenteral administration of thiamine hydrochloride and ascorbic acid concurrently with irradiation prevented the appearance of many of the general symptoms of irradiation sickness. It was found that nausea and vomiting were entirely eliminated. It is believed generally that thiamine is of value in the treatment of almost any disease in which chronic diarrhea occurs. It has been reported,<sup>93</sup> however, that it is of no value in the treatment of chronic ulcerative colitis. Veasey<sup>94</sup> discussed the use of vitamin B complex in the treatment of ophthalmic conditions. Cases in which beriberi heart resulting from deficiency of thiamine is cured after the administration of thiamine continue to be reported.<sup>95</sup>

In an interesting paper Laws<sup>96</sup> described a case of sensitization to thiamine hydrochloride. The patient (a woman) apparently was not

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90. Kaufman, R. E.: Influence of Thiamine on Blood Sugar Levels in Diabetic Patients, *Arch. Int. Med.* **66**:1079-1086 (Nov.) 1940. Wassmann, K.: Vitamin B<sub>1</sub> and Blood Sugar, *Acta med. Scandinav.* **106**:159-167, 1941. Trasoff, A., and Bordin, C.: The Use of Vitamin B<sub>1</sub> in Diabetes Mellitus: A Clinical Study, *Am. J. Digest. Dis.* **8**:1-2 (Jan.) 1941.

91. Fein, H. D.; Ralli, E. P., and Jolliffe, N.: Peripheral Neuropathy Due to Vitamin B<sub>1</sub> Deficiency in Diabetes Mellitus, *J. A. M. A.* **115**:1973-1976 (Dec. 7) 1940.

92. Wallace, W. S.: Studies in Radiation Sickness: II. Vitamins B<sub>1</sub> and C and the Small Intestinal Change in Radiation Sickness, *South. M. J.* **34**:170-173 (Feb.) 1941.

93. Shiffer, P., and Ferguson, L. K.: The Treatment of Idiopathic Ulcerative Colitis with Concentrated Liver Extract and Vitamin B<sub>1</sub>, *Am. J. Digest. Dis.* **8**:300-301 (Aug.) 1941.

94. Veasey, C. A., Jr.: Vitamin B in Ophthalmology, *Arch. Ophth.* **25**:450-468 (March) 1941.

95. Konstam, G., and Sinclair, H. M.: Cardiovascular Disturbances Caused by Deficiency of Vitamin B<sub>1</sub>, *Brit. Heart J.* **2**:231-240 (Oct.) 1940. Swan, W. G. A., and Laws, F.: A Case of Beri-Beri Heart, *ibid.* **2**:241-246 (Oct.) 1940.

96. Laws, C. L.: Sensitization to Thiamine Hydrochloride, *J. A. M. A.* **117**:176 (July 19) 1941.

sensitive to thiamine at the beginning of treatment, but after several injections she became so. About thirty minutes after one treatment her eyes and lips became edematous, large urticarial wheals appeared over the body and a feeling of tightness was experienced in the thorax; she became dyspneic and cyanotic and wheezed audibly. Epinephrine was administered within a few minutes, and at the end of five or six hours the entire reaction had subsided. Intradermal tests conducted with the commercial preparation of thiamine hydrochloride which had been used throughout the course of these injections produced a large urticarial wheal. Passive transfer was made to a nonallergic person, and at the end of forty-eight hours the sensitized sites reacted strongly when the same preparation of thiamine was introduced. A solution of thiamine hydrochloride prepared in water without the addition of other substance produced exactly the same type of reaction as did the commercial preparation, in which there was a preservative. This author suggested that it would be advisable to make intradermal tests with thiamine hydrochloride before administering it parenterally, particularly to patients who have received thiamine previously. Stiles<sup>97</sup> also pointed out that if it is desired to use intradermal tests for the detection of patients who have become hypersensitive to thiamine hydrochloride, more dilute preparations containing probably not more than 5 mg. per cubic centimeter should be used.

#### NICOTINIC ACID

*Chemical and Physiologic Properties.*—It has been known for some time that the cozymase content of animal tissues closely parallels the state of nicotinic acid nutrition, and there is no reason to believe that the same state of affairs does not exist among human beings. Whereas the administration of nicotinic acid has been shown invariably to raise the level of the factor V in human blood, the fact remains that these substances are not uniformly diminished in the blood of pellagrins. Axelrod, Spies and Elvehjem<sup>98</sup> recently showed that deficiency of nicotinic acid produced a marked diminution of coenzyme I in the striated muscle of human subjects, although only a slight effect was noted in the content of the erythrocytes in the blood of the same persons. Evaluation of the physiologic significance of this observation awaits the uncovering of additional knowledge concerning the quantitative relation between the coenzyme I content of human muscle and the ability of the muscle to carry out its oxidative functions. A decrease in the

97. Stiles, M. H.: Hypersensitivity to Thiamine, J. A. M. A. **117**:954 (Sept. 13) 1941; Hypersensitivity to Thiamine Chloride with a Note on Sensitivity to Pyridoxine Hydrochloride, J. Allergy **12**:507-509 (July) 1941.

98. Axelrod, A. E.; Spies, T. D., and Elvehjem, C. A.: The Effect of a Nicotinic Acid Deficiency upon the Coenzyme I Content of the Human Erythrocyte and Muscle, J. Biol. Chem. **138**:667-676 (April) 1941.

value for factor V in dog muscle, however, produces changes in its oxidative metabolism, and it may be expected that a similar relation is operative in human muscle. Although the importance of these observations cannot be overestimated, the authors advanced new problems in the same investigation by their observation that the antipellagra value of a compound does not necessarily parallel its ability to increase the coenzyme content of the tissues. Whereas the effect of nicotinic acid is marked in both respects, pyrazine monocarboxylic acid and pyridine betacarboxylic acid diethylamide (coramine) produced no consistent increase in values for coenzyme, despite clinical improvement among pellagrins. This agrees with the results of Dann and his co-workers,<sup>99</sup> who were unable to increase the content of the V factor in human blood by the administration of quinolinic acid and the pyrazine acids. These same substances failed to exhibit antiblacktongue activity in dogs, and these workers were inclined to doubt the antipellagra activity of the compounds. It is obvious, on the basis of these two papers alone, that there is still much to be learned about the pathologic physiology of pellagra.

Although the past year has been productive of much effort in such a direction, there is as yet no satisfactory laboratory procedure for the diagnosis of pellagra. Field and associates<sup>100</sup> presented an excellent review of this subject; they found estimates of the normal content of nicotinic acid in the blood to vary from 0.25 to 0.89 mg. per hundred cubic centimeters of whole blood. Values reported during the past year<sup>101</sup> are not in much better agreement than these figures. Much of this discrepancy is due to the use of different methods and to the fact that the chemical methods now in use are not specific for the detection of nicotinic acid. It is generally agreed that the major portion of the

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99. Dann, W. J.; Kohn, H. I., and Handler, P.: The Effect of Pyrazine Acids and Quinolinic Acid on the V-Factor Content of Human Blood and upon Canine Blacktongue, *J. Nutrition* **20**:477-490 (Nov.) 1940.

100. Field, H., Jr.; Melnick, D.; Robinson, W. D., and Wilkinson, C. F., Jr.: Studies on the Chemical Diagnosis of Pellagra (Nicotinic Acid Deficiency), *J. Clin. Investigation* **20**:379-386 (July) 1941.

101. (a) Kochhar, B. D.: The Quantitative Estimation of Nicotinic Acid in Blood and Other Body Fluids, *Indian J. M. Research* **28**:385-396 (Oct.) 1940; (b) Nicotinic Acid in Blood, *ibid.* **29**:133-136 (Jan.) 1941; (c) Nicotinic Acid in Blood and in Urine, *ibid.* **29**:341-350 (April) 1941. (d) Perlzweig, W. A.; Levy, E. D., and Sarett, H. P.: Nicotinic Acid Derivatives in Human Urine and Their Determination, *J. Biol. Chem.* **136**:729-745 (Dec.) 1940. (e) Briggs, A. P.: Excretion of Nicotinic Acid in Pellagra, *Proc. Soc. Exper. Biol. & Med.* **46**:374-378 (March) 1941. (f) Bandier, E.: The Nicotinic Acid Content of Blood and Urine, *Acta med. Scandinav.* **107**:62-79, 1941. (g) Isbell, H.; Wooley, J. G.; Butler, R. E., and Sebrell, W. H.: A Bacterial Assay Method for Nicotinamide and Related Substances in Blood, Urine, and Spinal Fluid, *J. Biol. Chem.* **139**:499-510 (June) 1941.

nicotinic acid is found in the erythrocytes and that determinations must be carried out on samples of whole blood.<sup>102</sup> Although normal values for nicotinic acid have varied widely in different reports, it is highly significant that there has been no important difference in these values reported for normal persons and those reported for pellagrins. Field and his associates<sup>100</sup> found a rather pronounced and consistent decrease in the urinary excretion of trigonelline (the form in which the greater part of nicotinic acid is excreted) among persons deficient in nicotinic acid, and they expressed the opinion that this observation may prove to be of value in the future. Kochhar<sup>101c</sup> and Perlzweig, Levy and Sarett<sup>101d</sup> conducted experiments on the excretion of nicotinic acid in the urine of human beings after the administration of test doses, but the value of this work cannot be assessed, since they used only normal persons. Kark and Meiklejohn<sup>103</sup> have produced additional evidence against porphyrinuria as a diagnostic adjunct in pellagra. They concluded on the basis of study of several cases that its appearance is coincidental and is dependent on hepatic dysfunction rather than on any essential part of pellagra.

Several articles in which new methods for the determination of nicotinic acid and its derivatives were explained appeared in the last year.<sup>104</sup> For those persons interested in the chemistry of nicotinic acid<sup>105</sup> we have listed two excellent reviews on this subject.

Mainzer and Krause<sup>100</sup> made the interesting observation that pellagrins, like patients suffering from Addison's disease, are hypersensitive to insulin and that prolonged and marked hypoglycemia occurs when they receive doses (5 units) which are otherwise ineffective. Among persons who had chronic pellagra this phenomenon persisted after cure

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102. Field, Melnick, Robinson and Wilkinson.<sup>100</sup> Footnotes 101 *a* and *f*.

103. Kark, R., and Meiklejohn, A. P.: *Pellegra and Porphyrinuria*, Am. J. M. Sc. **201**:380-385 (March) 1941.

104. Giri, K. V., and Naganna, B.: An Adsorption Method for the Estimation of Nicotinic Acid Content of Foodstuffs, Indian J. M. Research **29**:125-132 (Jan.) 1941. Stotz, E.: A Clinical Method of the Determination of Nicotinic Acid in Blood and Urine, J. Lab. & Clin. Med. **26**:1042-1046 (March) 1941. Swaminathan, M.: Further Studies on the Cyanogen Bromide Method of Estimating Nicotinic Acid in Biological Materials, Indian J. M. Research **29**:325-340 (April) 1941. Dann, W. J., and Handler, P.: The Quantitative Estimation of Nicotinic Acid in Animal Tissues, J. Biol. Chem. **140**:201-213 (July) 1941. Noll, C. I., and Jensen, O. G.: The Chemical Determination of Nicotinic Acid in Milk and Milk Derivatives, *ibid.* **140**:755-762 (Sept.) 1941.

105. Bacharach, A. L.: The Distribution of Nicotinic Acid in Human and Animal Foods, Nutrition Abstr. & Rev. **10**:459-465 (Jan.) 1941. Waisman, H. A., and Elvehjem, C. A.: Chemical Estimation of Nicotinic Acid and Vitamin B<sub>6</sub>, Indust. & Engin. Chem. (Analyt. Ed.) **13**:221-225 (April 15) 1941.

106. Mainzer, F., and Krause, M.: On Irreversible Functional Disturbances in Chronic Pellagra, Acta med. Scandinav. **104**:321-336, 1940.

or improvement, whereas among those who had acute pellagra cure was followed by restoration to normal of the response of the content of sugar in the blood to insulin. They concluded that qualitatively insufficient nutrition in some way produces irreversible injury to the homeostatic factors governing the content of sugar in the blood.

Petri and his associates<sup>107</sup> were able to produce pellagra in gastrectomized pigs, although the pigs had been fed a diet similar to that of hogs not operated on in which signs of deficiency did not develop. Neither nicotinic acid nor any other member of the vitamin B complex was effective in reversing the course of this type of pellagra in gastrectomized pigs or in arresting degeneration of nerve cells. The authors expressed the belief that this type of pellagra resembles the endogenous pellagra of man and concluded that the gastrectomized animals were unable to synthesize coenzymes from the available nicotinic acid.

Although others<sup>108</sup> have found nicotinic acid to be effective in reducing the clotting time of blood of patients who have febrile disease, Aggeler and Lucia<sup>109</sup> could not demonstrate a coagulant effect when this acid was tested in vitro with heparinized recalcified plasma. They observed that nicotinic acid is an active hemolytic agent and suggested that its coagulant effect is dependent on the release of thromboplastin from the disrupted elements of the blood, since nonhemolytic compounds of nicotinic acid were quite ineffective in promoting the coagulation of blood.

*Clinical Use.*—We feel that any review of the literature on nicotinic acid would be incomplete without mention of several excellent and complete summaries of the subject which will serve to bring the reader up to date,<sup>110</sup> although they are not strictly contributions in that they

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107. Petri, S.; Nørgaard, F., and Bandier, E.: Studies on the Causation of Experimental Gastroprival Pellagra: Therapeutic Experiment (Ib) with Preventive Peroral and Parenteral Administration of Nicotinic Acid, *Acta med. Scandinav.* **103**:584-606, 1940; Studies on the Causation of Experimental Gastroprival Pellagra: Therapeutic Experiment (II) with Preventive Parenteral Administration of Vitamin B<sub>1</sub>, Riboflavin and Vitamin A, Separately and in the Combination Vitamin B<sub>1</sub> + Vitamin A, *ibid.* **104**:245-260, 1940.

108. Calder, R. M., and Kerby, G. P.: The Effect of Nicotinic Acid on Blood Coagulation, *Am. J. M. Sc.* **200**:590-596 (Nov.) 1940.

109. Aggeler, P. M., and Lucia, S. P.: Action of Nicotinic Acid on Coagulation of the Blood, *Proc. Soc. Exper. Biol. & Med.* **47**:522-525 (June) 1941.

110. Sydenstricker, V. P.: The Clinical Manifestations of Nicotinic Acid and Riboflavin Deficiency (Pellagra), *Ann. Int. Med.* **14**:1499-1517 (March) 1941; The Present Status of Nicotinic Acid, *Arch. Int. Med.* **67**:746-754 (April) 1941. Jolliffe, N.; Wortis, H., and Stein, M. H.: Vitamin Deficiencies and Liver Cirrhosis in Alcoholism: IV. The Wernicke Syndrome; V. Nicotinic Acid Deficiency Encephalopathy; VI. Encephalopathies with Possible Nutritional Involvement, *Quart. J. Stud. on Alcohol* **2**:73-97 (June) 1941.

do not offer anything new. In addition to these, Harris<sup>111</sup> has presented an exhaustive treatise on pellagra in his book "Clinical Pellagra."

Kooser and Blankenhorn<sup>112</sup> conducted an interesting survey among the residents of two adjacent communities in Kentucky, one mining and one rural, in both of which pellagra was once endemic. Persons of the two groups had been similar in economic status and food habits prior to a campaign of education in the health-sparing value of foods in the rural community. A study of the dietary habits of persons of the two groups revealed little difference in the consumption of pellagra-producing foods, but there was a significant increase in the pellagra-preventing foods eaten by members of the rural group. The result apparently was the complete eradication of pellagra in members of the rural group, whereas it was still endemic in the mining community, despite no change in economic status, at the time of the report by Kooser and Blankenhorn. The importance of this study cannot be overestimated from a public health standpoint.

Sydenstricker and Cleckley<sup>113</sup> presented data concerning 29 patients who had varying psychotic reactions, including lethargy, stupor, mania, hallucination and disorientation, all of whom exhibited a prompt response to nicotinic acid therapy. As the authors noted, the conditions of these patients do not fit into a single psychiatric classification but include that group "ordinarily diagnosed as toxic psychosis, exhaustion delirium, or perhaps, psychosis, type undetermined." Despite the complete lack of any evidence of pellagra, the response to the administration of nicotinic acid was remarkable in all cases, being usually prompt and often spectacular. The authors were led to express the belief that the psychotic symptoms manifested in these various disturbances have a basis in avitaminosis. In discussing this presentation, Aring made the interesting observation that the response of the patient to nicotinic acid possibly was referable not to the action of the acid as a vitamin but to its action as a vasodilator, with the resulting increased cerebral circulation. This suggestion is at variance, however, with the observations of Loman and his associates,<sup>114</sup> who administered nicotinic acid intravenously to human beings by way of the carotid and the brachial artery and reported the following results: 1. The pressure of the cerebrospinal fluid was insignificantly altered. 2. The caliber of the retinal vessels was unchanged.

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111. Harris, S.: *Clinical Pellagra*, St. Louis, C. V. Mosby Company, 1941.

112. Kooser, J. H., and Blankenhorn, M. A.: *Pellagra and the Public Health: A Dietary Survey of Kentucky Mountain Folk in Pellagrous and in Non-Pellagrous Communities*, J. A. M. A. **116**:912-915 (March 8) 1941.

113. Sydenstricker, V. P., and Cleckley, H. M.: *The Effect of Nicotinic Acid in Stupor, Lethargy and Various Other Psychiatric Disorders*, Am. J. Psychiat. **98**:83-92 (July) 1941.

114. Loman, J.; Rinkel, M., and Myerson, A.: *The Intracranial and Peripheral Vascular Effects of Nicotinic Acid*, Am. J. M. Sc. **202**:211-216 (Aug.) 1941.

3. The cerebral blood flow, as determined by arteriovenous differences in oxygen content, was only slightly increased, whereas the flow to the arm was markedly increased. These same authors have suggested the possible usefulness of nicotinic acid in the treatment of Raynaud's disease, since it shortens the Raynaud-like response produced by epinephrine when both drugs are injected simultaneously into the brachial artery.

Smith and her associates<sup>115</sup> described a syndrome involving sebaceous glands which they found to be frequently associated with pellagra and which they have termed "dyssebacia." The lesions are found chiefly on the face and consist of plugs of inspissated sebum projecting from the sebaceous follicles, producing a "sandpaper" appearance. Microscopically, hyperplasia of the sebaceous glands, with dilatation and plugging of the follicles, is evident. Nicotinic acid was curative in most cases, although it was not so effective as yeast or crude extracts of liver.

#### RIBOFLAVIN

*Chemical and Physiologic Properties.*—Since the yellow enzyme, of which riboflavin is a constituent, is concerned in part with carbohydrate metabolism, it has long been felt that deficiency of this substance, like deficiency of thiamine, should result in some changes in the nervous system. It has been established that in acute riboflavin deficiency in dogs profound collapse occurs within one hundred to one hundred and fifty days after institution of the diet deficient in riboflavin and that this condition can be treated successfully by prompt administration of the missing factor. These animals do not exhibit specific neurologic disturbances. In a recent paper, however, Street and his associates<sup>116</sup> reported that long subsistence on a diet low in riboflavin leads to the development of neurologic abnormalities in dogs, as evidenced by clumsiness and, finally, by loss of the deep reflexes of the limbs. These symptoms are accompanied by myelin degeneration of the peripheral nerves and of the posterior columns of the spinal cord. These changes become more extensive as the period of subsistence on the deficient diet continues. Apparently, the levels of urea nitrogen, nonprotein nitrogen, uric acid and hemoglobin in the blood are not affected in the presence of riboflavin deficiency in dogs.<sup>117</sup> However, a decrease of 27 per cent in the values for riboflavin in the blood was found in dogs in acute

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115. Smith, S. G.; Smith, D. T., and Callaway, J. L.: Dysfunction of the Sebaceous Glands Associated with Pellagra, *J. Invest. Dermat.* **4**:23-42 (Feb.) 1941.

116. Street, H. R.; Cowgill, G. R., and Zimmerman, H. M.: Further Observations of Riboflavin Deficiency in the Dog, *J. Nutrition* **22**:7-24 (July) 1941.

117. Axelrod, A. E.; Lipton, M. A., and Elvehjem, C. A.: Riboflavin Deficiency in the Dog, *Am. J. Physiol.* **133**:555-561 (July) 1941.

stages of deficiency, and the average daily urinary excretion of riboflavin by these animals was markedly reduced.

In contrast, deficiency of riboflavin in the pig is characterized clinically by retarded growth, corneal opacities, changes in the skin and hair and collapse, sometimes associated with hypoglycemia.<sup>118</sup> In an excellent paper by Patek and his associates, it was observed that 4 pigs subsisting on the basal diet collapsed in three, six, seven and ten months, respectively, after the experimental feeding was begun. The pigs suddenly became listless and refused to eat. The extremities became cold and cyanotic, and the animals were found in a state of collapse. Two of the animals were revived by the parenteral administration of riboflavin. One received 100 mg. intravenously three hours after the onset of collapse, and 1 received 200 mg. intravenously nearly two hours after the onset of collapse. The response to these injections was dramatic. The animals suddenly grunted, stood up, walked and ate their food. They were unsteady on their hindlegs for several days, however, after which the ataxia disappeared. Hypoglycemia was present throughout the collapse syndrome, but some data suggested that this syndrome was not the direct result of hypoglycemia. The authors pointed out that it is possible that deficiency of riboflavin interferes with the proper utilization of dextrose. It has also been reported<sup>119</sup> that riboflavin metabolism is intimately connected with fat metabolism in growing animals.

Apparently, riboflavin alone affords no significant protection against hepatic cancer caused by the administration of butter yellow (dimethylaminoazobenzene). When nicotinic acid was combined with riboflavin, however, a decrease of 50 per cent in the incidence of cancer resulted and when casein was administered as an additional supplement (to 200 micrograms of riboflavin given daily) the protective effect was striking, although not absolute.<sup>120</sup>

Several methods<sup>121</sup> have been employed for the determination of riboflavin. General discussion and comparison of these various methods

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118. Patek, A. J., Jr.; Post, J., and Victor, J.: Riboflavin Deficiency in the Pig, *Am. J. Physiol.* **133**:47-55 (May) 1941.

119. Mannering, G. J.; Lipton, M. A., and Elvehjem, C. A.: Relation of Dietary Fat to Riboflavin Requirement of Growing Rats, *Proc. Soc. Exper. Biol. & Med.* **46**:100-104 (Jan.) 1941.

120. Kensler, C. J.; Sugiura, K.; Young, N. F.; Halter, C. R., and Rhoads, C. P.: Partial Protection of Rats by Riboflavin with Casein Against Liver Cancer Caused by Dimethylaminoazobenzene, *Science* **93**:308-310 (March 28) 1941.

121. Wagner, J. R.; Axelrod, A. E.; Lipton, M. A., and Elvehjem, C. A.: A Rat Assay Method for the Determination of Riboflavin, *J. Biol. Chem.* **136**:357-364 (Nov.) 1940. Lingane, J. J., and Davis, O. L.: Polarographic Determination of Riboflavin (Vitamin B<sub>2</sub>) and Other Vitamin B Factors, *ibid.* **137**:567-574 (Feb.) 1941. Van Duyne, F. O.: A Method for the Determination in Vitro of Riboflavin in Tissues, *ibid.* **139**:207-218 (May) 1941.



also have been reported.<sup>122</sup> Improvements in each of these methods have been suggested.

*Clinical Deficiency.*—Since the clinical manifestations of riboflavin deficiency were described, considerable effort has been made to discover some method by which this deficiency in man could be measured by laboratory methods. Axelrod and his associates<sup>123</sup> analyzed the values for riboflavin in the blood of 20 normal persons and similar values in a group of 35 patients who had varying degrees of riboflavin deficiency. Moreover, study of riboflavin in the muscles was carried out on 9 control subjects and on 30 patients who had pellagra. On the basis of their results, the authors concluded that determinations of riboflavin in the blood and muscle are of little significance in the evaluation of riboflavin deficiency in man. On the other hand, Axelrod and his group<sup>124</sup> in another study found that the determination of the daily excretion of riboflavin in the urine served as an aid in appraisal of the degree of riboflavin deficiency. It was shown that from 30 to 40 per cent of the vitamin was excreted in the urine of 3 persons within one hour after each had received 200 micrograms of riboflavin per kilogram of body weight. Forty-two per cent of the injected riboflavin was excreted within three hours by persons who received 400 micrograms of the vitamin per kilogram of body weight. Strong and his associates<sup>125</sup> found that the daily urinary excretion of riboflavin by normal adult human beings subsisting on an unrestricted diet amounted to 500 to 800 micrograms.

Although riboflavin is not abundant in many foods other than milk and meat, it has been reported<sup>126</sup> that it is present in citrus fruits, such as oranges and grapefruit, and in bananas and tomatoes but that little of it is found in apples or pears. Sydenstricker, Kelly and Weaver<sup>127</sup> recently reviewed the entire problem of ariboflavinosis. These investigators pointed out that any condition which interferes with the

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122. Emmett, A. D.; Bird, O. D.; Brown, R. A.; Peacock, G., and Vandembelt, J. M.: Determination of Vitamin B<sub>2</sub> (Riboflavin): Comparison of Bioassay, Microbiological, and Fluorometric Methods, *Indust. & Engin. Chem. (Analyt. Ed.)* **13**:219-221 (April 15) 1941.

123. Axelrod, A. E.; Spies, T. D., and Elvehjem, C. A.: Riboflavin Content of Blood and Muscle in Normal and in Malnourished Humans, *Proc. Soc. Exper. Biol. & Med.* **46**:146-149 (Jan.) 1941.

124. Axelrod, A. E.; Spies, T. D.; Elvehjem, C. A., and Axelrod, V.: A Study of Urinary Riboflavin Excretion in Man, *J. Clin. Investigation* **20**:229-232 (March) 1941.

125. Strong, F. M.; Feeney, R. E.; Moore, B., and Parsons, H. T.: The Riboflavin Content of Blood and Urine, *J. Biol. Chem.* **137**:363-372 (Jan.) 1941.

126. Lanford, C. F.; Finkelstein, B., and Sherman, H. C.: Riboflavin Content of Some Typical Fruits, *J. Nutrition* **21**:175-177 (Feb.) 1941.

127. Sydenstricker, V. P.; Kelly, A. R., and Weaver, J. W.: Ariboflavinosis, with Special Reference to the Ocular Manifestations, *South. M. J.* **34**:165-170 (Feb.) 1941.

proper absorption and assimilation of riboflavin may produce riboflavin deficiency. Under experimental conditions, the authors found that the injection of large amounts of nicotinic acid into patients subsisting on a diet deficient in riboflavin seemed to increase the requirement of riboflavin and to precipitate the signs of ariboflavinosis. The authors suggested that this phenomenon probably explains the high incidence of relapse among pellagrins treated with nicotinic acid without improvement of the diet. Many symptoms reported by patients who have a deficiency of riboflavin are common to all types of avitaminoses and probably are the results of multiple deficiency. Although soreness of the lips and tongue and dysphagia due to painful fissures of the commissures of the lip and tenderness of the tongue are characteristic, the authors wrote that ocular symptoms have nevertheless preceded all others among more than half their patients and that they occurred at some time among more than 90 per cent of them. Burning and itching of the eyes, photophobia, lacrimation, rapid visual fatigue, blurred vision and poor distant vision and inability to see distinctly in dim light are common specific symptoms. Usually, 5 mg. of riboflavin taken daily by mouth is adequate for rapid cure, but in the presence of gastric achlorhydria, diarrhea or severe hepatic disease 10 or 15 mg. daily may be required. In some cases the parenteral administration of 10 to 15 mg. of sodium riboflavin may be necessary. After the administration of riboflavin Sydenstricker, Kelly and Weaver observed rapid symptomatic improvement in a group of some 120 patients. Photophobia often is relieved after seventy-two hours of treatment. Glossitis is the first anatomic lesion to show changes. In a great majority of instances the tongue is restored to normal color by the third day of medication. These authors in conclusion pointed out that thus far it seems that superficial, vascular keratitis is the earliest and the most common visible manifestation of riboflavin deficiency and that it is also a rather reliable index of early deficiency of the B group of vitamins.

An interesting clinical study of riboflavin deficiency among infants and children was made by Spies and his associates.<sup>128</sup> These authors reported clinical, laboratory and dietary studies on 241 infants and children who had characteristic riboflavin deficiency. The authors expressed the belief that it is the most common clinical deficiency disease among infants and children in the particular area in Alabama in which deficiency diseases in general are endemic. It was pointed out that the mothers of the children studied usually had subsisted on inadequate diets during pregnancy and lactation; interestingly enough, specific treatment of a mother with riboflavin or substance rich in riboflavin was curative

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128. Spies, T. D.; Bean, W. B.; Vilter, R. W., and Huff, N. E.: Endemic Riboflavin Deficiency in Infants and Children, *Am. J. M. Sc.* **200**:697-701 (Nov.) 1940.

for the lesions in her nursing infant. The authors observed that the average patient responded satisfactorily to the oral administration of 1 mg. of riboflavin three times a day or 1 ounce (29.6 cc.) of brewers' yeast or liver extract administered daily.

Ocular lesions resulting from deficiency of riboflavin are common among the Chinese. Only in a few cases (14 per cent of 36 cases) was cheilosis or glossitis present, and when present it was mild, according to Hou.<sup>129</sup> These observations differ from those reported by Sydenstricker and associates, who found that the majority of their patients who had ocular symptoms also suffered concomitantly from lesions of the lips and tongue. This same Chinese author<sup>130</sup> later, however, reported that cheilosis is common among Chinese refugees. Forty-four per cent of the children examined in a refugee camp were so affected.

Johnson and Eckardt<sup>131</sup> treated a number of patients who had active and inactive syphilitic keratitis for more than a year with riboflavin in doses of 6 to 9 mg. daily. Although these authors stressed the usefulness of riboflavin in the metabolism of tissues like the cornea and although they advised the administration of the vitamin B complex as supportive treatment in all forms of corneal ulcer, they did not find that riboflavin administered over this long period was of value in the treatment of syphilitic keratitis. A full discussion of the use of riboflavin in the treatment of keratitis and associated conditions was given by Benedict and Wagener.<sup>132</sup>

#### VITAMIN B<sub>6</sub> (PYRIDOXINE)

*Chemical and Physiologic Properties.*—Waisman and Elvehjem<sup>133</sup> reviewed the chemical methods for the estimation of pyridoxine. In addition, new chemical<sup>134</sup> and biologic<sup>135</sup> methods have been described.

129. Hou, H. C.: Riboflavin Deficiency Among Chinese: I. Ocular Manifestations, Chinese M. J. **58**:616-628 (Dec.) 1940.

130. Hou, H. C.: Riboflavin Deficiency Among Chinese: II. Cheilosis and Seborrheic Dermatitis, Chinese M. J. **59**:314-325 (April) 1941.

131. Johnson, L. V., and Eckardt, R. E.: Is the Onset of Interstitial Keratitis Related to Riboflavin Deficiency? Arch. Ophth. **23**:631-632 (March) 1940; Rosacea Keratitis and Conditions with Vascularization of Cornea Treated with Riboflavin, *ibid.* **23**:899-907 (May) 1940; Ocular Conditions Associated with Clinical Riboflavin Deficiency, *ibid.* **24**:1001-1005 (Nov.) 1940.

132. Benedict, W. L., and Wagener, H. P.: Ophthalmology: Progress in Medical Science; Riboflavin and Keratitis, Am. J. M. Sc. **201**:303-309 (Feb.) 1941.

133. Waisman, H. A., and Elvehjem, C. A.: Chemical Estimation of Nicotinic Acid and Vitamin B<sub>6</sub>, Indust. & Engin. Chem. (Analyt. Ed.) **13**:221-225 (April 15) 1941.

134. Swaminathan, M.: A Chemical Test for Vitamin B<sub>6</sub> in Foods, Indian J. M. Research **28**:427-439 (Oct.) 1940. Scudi, J. V.; Unna, K., and Antopol, W.: A Study of the Urinary Excretion of Vitamin B<sub>6</sub> by a Colorimetric Method, J.

Henderson and his associates<sup>136</sup> have shown that the distribution of vitamin B<sub>6</sub> in foods is similar to the distribution in such foods of the other members of the vitamin B complex; kidney and muscle would appear to be the richest sources of this factor. Several other articles in which the chemistry of pyridoxine is considered are listed here by title.<sup>137</sup>

Experimental investigations in animals have not produced remarkable results. Street and his co-workers<sup>138</sup> produced severe microcytic anemia in dogs sustained on a diet deficient in vitamin B<sub>6</sub>. This anemia regressed when vitamin B<sub>6</sub> was administered but did not regress when ferrous sulfate was administered. After three hundred days symptoms of cardiac decompensation, with dilatation and failure of the right ventricle, developed in the dogs. This is the picture usually associated with beriberi among human beings, but all of these animals had received sufficient thiamine.

Gross<sup>139</sup> investigated acrodynia in rats and its relation to pyridoxine, the filtrate factor and the essential fatty acids. He showed that the administration of any of these factors singly will not prevent some of the characteristic lesions of acrodynia and that vitamin B<sub>6</sub> exerts a curative action only when the animals are maintained on sufficient amounts of essential fatty acids. This agrees with the observations of György and Eckardt,<sup>140</sup> who have classified the cutaneous lesions of

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Biol. Chem. **135**:371-376 (Sept.) 1940. Scudi, J. V.: On the Colorimetric Determination of Vitamin B<sub>6</sub>, *ibid.* **139**:707-720 (June) 1941.

135. Conger, T. W., and Elvehjem, C. A.: The Biological Estimation of Pyridoxine (Vitamin B<sub>6</sub>), *J. Biol. Chem.* **138**:555-561 (April) 1941.

136. Henderson, L. M.; Waisman, H. A., and Elvehjem, C. A.: The Distribution of Pyridoxine (Vitamin B<sub>6</sub>) in Meat and Meat Products, *J. Nutrition* **21**:589-598 (June) 1941.

137. Scudi, J. V.; Bastedo, W. A., and Webb, T. J.: The Formation of a Vitamin B<sub>6</sub>-Borate Complex, *J. Biol. Chem.* **136**:399-406 (Nov.) 1940. Harris, S. A.; Webb, T. J., and Folkers, K.: Chemistry of Vitamin B<sub>6</sub>: I. Tautomerism, *J. Am. Chem. Soc.* **62**:3198-3203 (Nov.) 1940. Harris, S. A.: Chemistry of Vitamin B<sub>6</sub>: II. Reactions and Derivatives, *ibid.* **62**:3203-3205 (Nov.) 1940. Harris, S. A., and Wilson, A. N.: Chemistry of Vitamin B<sub>6</sub>: III. 2-Methyl-3-Hydroxy-4, 5-Bis-(Hydroxymethyl)-Pyridine; a Homolog of Vitamin B<sub>6</sub>, *ibid.* **63**:2526-2527 (Sept.) 1941.

138. Street, H. R.; Cowgill, G. R., and Zimmerman, H. M.: Some Observations of Vitamin B<sub>6</sub> Deficiency in the Dog, *J. Nutrition* **21**:275-290 (March) 1941.

139. Gross, P.: The Role of the Unsaturated Fatty Acids in the Acrodynia (Vitamin B<sub>6</sub> Deficiency) of the Albino Rat, *J. Invest. Dermat.* **3**:505-522 (Dec.) 1940.

140. György, P., and Eckardt, R. E.: Further Investigations on Vitamin B<sub>6</sub> and Related Factors of the Vitamin B<sub>2</sub> Complex in Rats, *Biochem. J.* **34**:1143-1154 (Sept.) 1940.

the disease into three types, which regularly appear in rats fed vitamin B<sub>6</sub> without the addition of other members of the B complex. The relation of pyridoxine and the filtrate factor was further emphasized by Sullivan and Nicholls,<sup>141</sup> who observed severe and even gangrenous changes in the extremities of animals deficient in this vitamin.

Unna and Greslin<sup>142</sup> were unable to observe any toxic reaction in dogs, rabbits and rats unless the vitamin was administered in doses much larger than those ordinarily employed clinically.

*Clinical Use.*—There is a state of complete controversy concerning the effectiveness of vitamin B<sub>6</sub> in the treatment of Parkinson's disease. Supplementing previous observations, Jolliffe<sup>143</sup> reported definite subjective and objective improvement in 4 of 15 cases. All his failures occurred in cases in which the patient had some type of disability of more than three years' duration or in which a history of encephalitis had been given. Baker<sup>144</sup> observed objective improvement in 6 of 15 cases in which pyridoxine was administered intravenously and also improvement in 2 of 4 cases in which the factor was given by mouth. In direct contrast to these results, Zeligs<sup>145</sup> failed completely to notice any beneficial effect from administration of the factor in 15 selected cases. Barker and his associates<sup>146</sup> have done some accurate and well controlled work on this subject, and in 7 cases they were unable to observe "the slightest evidence of objective improvement." In addition, they investigated the urinary excretion of pyridoxine by Scudi's method and found this value to be within normal limits in all cases. Flexner and Chassin<sup>147</sup> found low values for the excretion of pyridoxine in 6 of 7 cases in which post-encephalitic parkinsonism was present. This is not, however, in agreement with the clinical observations of Jolliffe.

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141. Sullivan, M., and Nicholls, J.: Nutritional Dermatoses in the Rat: III. Gangrene and Spontaneous Amputation of the Digits Produced by the Combined Deficiency of Vitamin B<sub>6</sub> and the Filtrate Components, *J. Invest. Dermat.* **4**:123-133 (April) 1941.

142. Unna, K., and Greslin, J.: Studies on the Toxicity and Pharmacology of Vitamin B<sub>6</sub> (2-Methyl-3-Hydroxy-4, 5, Bis-(Hydroxymethyl)-Pyridine), *J. Pharmacol. & Exper. Therap.* **70**:400-407, (Dec.) 1940.

143. Jolliffe, N.: Effects of Vitamin B<sub>6</sub> in Paralysis Agitans, *Tr. Am. Neurol. A.* **66**:54-59, 1940.

144. Baker, A. B.: Treatment of Paralysis Agitans with Vitamin B<sub>6</sub> (Pyridoxine Hydrochloride), *J. A. M. A.* **116**:2484-2487 (May 31) 1941.

145. Zeligs, M. A.: Use of Pyridoxine Hydrochloride (Vitamin B<sub>6</sub>) in Parkinsonism, *J. A. M. A.* **116**:2148-2149 (May 10) 1941.

146. Barker, W. H.; Stein, H. J.; Miller, M. H., and Wintrobe, M. M.: Failure of Pyridoxine (Vitamin B<sub>6</sub>) to Modify the Parkinsonian Syndrome, *Bull. Johns Hopkins Hosp.* **69**:266-275 (Sept.) 1941.

147. Flexner, J., and Chassin, M. R.: Clinical Studies on Pyridoxine (Vitamin B<sub>6</sub>), *J. Clin. Investigation* **20**:313-316 (May) 1941.

Antopol and Schotland<sup>148</sup> administered pyridoxine to 6 patients who had pseudohypertrophic muscular dystrophy and claimed to have effected much improvement thereby. This is a problem which obviously will have to be investigated further.

#### PANTOTHENIC ACID

The literature of the past year on pantothenic acid is completely devoid of interest to the practicing physician who is seeking a substance that will aid in the treatment of his patients. No one has come forward with any evidence that a deficiency of this factor occurs among human beings, and such experimental work as has been done has been limited to animals.

Much confusion exists concerning the identity of pantothenic acid in relation to the liver filtrate factor, and a few writers have come to use the two terms interchangeably. Although the work of Lythgoe and his associates<sup>149</sup> suggests that these factors are identical, the great bulk of evidence seems to indicate that such is not the case.<sup>150</sup> Emerson and Evans<sup>150a</sup> have shown that pantothenic acid alone will alleviate some of the symptoms caused by deficiency of the liver filtrate factor in rats but that it is not so effective as a dose of the filtrate factor containing an equal amount of pantothenic acid. These observations are in general agreement with those of other investigators.<sup>151</sup>

Rather than become involved in a long discussion of individual experiments with animals, it seems wiser simply to list here the various results obtained and to refer the reader to the respective articles concerned. Pantothenic acid has been shown (1) to promote growth in

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148. Antopol, W., and Schotland, C. E.: The Use of Vitamin B<sub>6</sub> in Pseudohypertrophic Muscular Dystrophy, *J. A. M. A.* **114**:1058-1059 (March 23) 1940.

149. Lythgoe, B.; Macrae, T. F.; Stanley, R. H.; Todd, A. R., and Work, C. E.: The Vitamin B<sub>2</sub> Complex of Liver: The Identity of the Liver Filtrate Factor with Pantothenic Acid, *Biochem. J.* **34**:1335-1340 (Nov.) 1940.

150. (a) Emerson, G. A., and Evans, H. M.: Growth and Graying of Rats with Total "Filtrate Factor" and with Pantothenic Acid, *Proc. Soc. Exper. Biol. & Med.* **46**:655-658 (April) 1941. (b) Dimick, M. K., and Lepp, A.: Relation of Pantothenic Acid to the Filtrate Fraction of the Vitamin B Complex, *J. Nutrition* **20**:413-426 (Nov.) 1940. (c) Unna, K.: Pantothenic Acid Requirement of the Rat, *ibid.* **20**:565-576 (Dec.) 1941.

151. (a) Unna, K.: Effect of Pantothenic Acid on Growth and Reproduction of Rats on Synthetic Diet, *Am. J. M. Sc.* **200**:848 (Dec.) 1940. (b) György, P., and Poling, C. E.: Further Experiments on Nutritional Achromotrichia in Rats and Mice, *Proc. Soc. Exper. Biol. & Med.* **45**:773-776 (Dec.) 1940. (c) Frost, D. V.; Moore, R. C., and Dann, F. P.: Effect of Pantothenic Acid Alone and in Natural Products on Nutritional Achromotrichia in Rats, *ibid.* **46**:507-511 (March) 1941. (d) Footnote 150 b and c.

rats,<sup>152</sup> mice<sup>153</sup> and chicks<sup>150b</sup>; (2) to prevent and cure some of the lesions of nutritional achromotrichia in rats,<sup>154</sup> and (3) to prevent adrenal hemorrhage and necrosis in rats.<sup>155</sup>

Unna and Greslin<sup>156</sup> studied the toxicity of pantothenic acid in various animals and found that it resembled other members of the vitamin B complex in its low toxicity.

McElroy and Goss,<sup>157</sup> in a study of the contents of the rumina of sheep and cows, found that samples of these contents contained twenty to thirty times as much pantothenic acid as the amounts that had been fed to the animals. Furthermore, they found twice as much pantothenic acid in the milk excreted by one cow as could be accounted for in the ration the cow had been fed.

Pelczar and Porter<sup>158</sup> presented a microbiologic technic for the determination of pantothenic acid and studied the values for this factor in the blood of normal human beings. They found that such values ranged from 0.030 to 0.099 microgram per cubic centimeter of blood,

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152. (a) Zschiesche, E., and Mitchell, H. K.: Pantothenic and Hydroxy-Pantothenic Acids in Animal Nutrition, *Proc. Soc. Exper. Biol. & Med.* **45**:565-567 (Nov.) 1940. (b) Sandza, J. G., and Cerecedo, L. R.: Requirement of the Mouse for Pantothenic Acid and for a New Factor of the Vitamin B Complex, *J. Nutrition* **21**:609-615 (June) 1941. (c) Emerson and Evans.<sup>150a</sup> Footnote 151 *a* and *b*.

153. Lippincott, S. W., and Morris, H. P.: Pathological Changes in the Mouse Due to Pantothenic Acid Deficiency, *Am. J. Path.* **17**:588-589 (July) 1941. György and Poling.<sup>151b</sup> Sandze and Cerecedo.<sup>152b</sup>

154. Unna, K., and Sampson, W. L.: Effect of Pantothenic Acid on the Nutritional Achromotrichia, *Proc. Soc. Exper. Biol. & Med.* **45**:309-311 (Oct.) 1940. Wooley, D. W.: Relationship of Pantothenic Acid and Inositol to Alopecia in Mice, *ibid.* **46**:565-569 (April) 1941. Emerson and Evans.<sup>150a</sup> Frost, Moore and Dann.<sup>151c</sup>

155. Mills, R. C.; Shaw, J. H.; Elvehjem, C. A., and Phillips, P. H.: Curative Effect of Pantothenic Acid on Adrenal Necrosis, *Proc. Soc. Exper. Biol. & Med.* **45**:482-484 (Oct.) 1940. Salmon, W. D., and Engel, R. W.: Pantothenic Acid and Hemorrhagic Adrenal Necrosis in Rats, *ibid.* **45**:621-623, (Nov.) 1940.

156. Unna, K., and Greslin, J.: Toxicity of Pantothenic Acid, *Proc. Soc. Exper. Biol. & Med.* **45**:311-312 (Oct.) 1940; Studies on the Toxicity and Pharmacology of Pantothenic Acid, *J. Pharmacol. & Exper. Therap.* **73**:85-90 (Sept.) 1941.

157. McElroy, L. W., and Goss, H.: A Quantitative Study of Vitamins in the Rumen Content of Sheep and Cows Fed Vitamin-Low Diets: IV. Pantothenic Acid, *J. Nutrition* **21**:405-409 (April) 1941.

158. Pelczar, M. J., Jr., and Porter, J. R.: A Microbiological Assay Technique for Pantothenic Acid with the Use of "Proteus Morganii," *J. Biol. Chem.* **139**:111-119 (May) 1941; Determination of Pantothenic Acid in Normal Blood and Urine by Microbiological Technic, *Proc. Soc. Exper. Biol. & Med.* **47**:3-7 (May) 1941.

with an average value of 0.059 microgram per cubic centimeter, and that the normal daily excretion of pantothenic acid in the urine varied from 1.46 to 6.79 mg., with an average value for such excretion of 3.81 mg.

#### ASCORBIC ACID (VITAMIN C)

*Chemical and Physiologic Properties.*—Last year two of us (H. R. B. and W. V. L.) reviewed several articles in which strong evidence was presented that ascorbic acid had an enzyme function. Results of subsequent investigations have placed this possibility on even stronger ground. Levine, Marples and Gordon<sup>159</sup> have shown that if premature infants are fed diets relatively high in protein they exhibit a spontaneous defect in their metabolism of tyrosine and phenylalanine, excreting l-parahydroxyphenyllactic acid and parahydroxyphenylpyruvic acid in the urine, rather than homogentisic acid, as in the case of alkaptonuria. They were able to remedy this metabolic defect promptly by the administration of ascorbic acid.<sup>160</sup> In the course of their efforts to prove the specificity of ascorbic acid in abolishing this metabolic error, they were unable to demonstrate any similar effect exerted by other substances, including all members of the vitamin B complex. Sealock, Perkinson and Basinski<sup>161</sup> supplemented these observations with results obtained in investigations on animals and demonstrated that vitamin C had a parallel function in guinea pigs. Rothman<sup>162</sup> has shown ascorbic acid to have an influence in vitro on the oxidation and oxidation products of tyrosine in that it greatly furthers the formation of dihydroxyphenylalanine (dopa) and prevents its further oxidation. There seems to be justification, then, for the statement by Levine, Gordon and Marples<sup>160</sup> that these "observations do establish beyond any doubt the key position of vitamin C in the metabolism of aromatic amino acids in the growing human organism." They expressed the belief that the detection of the various intermediary products in the urine may serve as a valuable aid in the early detection of deficiency of vitamin C among premature and young infants and that disappearance of such products from the urine may serve as the earliest sign of healing.

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159. Levine, S. Z.; Marples, E., and Gordon, H. H.: A Defect in the Metabolism of Tyrosine and Phenylalanine in Premature Infants: I. Identification and Assay of Intermediary Products, *J. Clin. Investigation* **20**:199-207 (March) 1941.

160. Levine, S. Z.; Gordon, H. H., and Marples, E.: A Defect in the Metabolism of Tyrosine and Phenylalanine in Premature Infants: II. Spontaneous Occurrence and Eradication by Vitamin C, *J. Clin. Investigation* **20**:209-219 (March) 1941.

161. Sealock, R. R.; Perkinson, J. D., Jr., and Basinski, D. H.: Further Analysis of the Rôle of Ascorbic Acid in Phenylalanine and Tyrosine Metabolism, *J. Biol. Chem.* **140**:153-160 (July) 1941.

162. Rothman, S.: Influence of Ascorbic Acid on Oxidation of Tyrosine by Ultraviolet Light, *Proc. Soc. Exper. Biol. & Med.* **45**:52-54 (Oct.) 1940.



Whether this will prove to be the case is obviously a subject concerning which nothing more than conjecture can be exercised now; it seems apparent, however, that the time is not far distant when investigators will present answers to the problem of the fundamental role of vitamin C in the metabolism of the body. In this same paper<sup>160</sup> are offered some of the new questions which arise as a direct result of this work:

What is the relation, if any, between the demonstrated defect in the metabolism of tyrosine and phenylalanine and the morphologic changes characteristic of vitamin C deficiency, namely, improper formation of intercellular substance and collagen? Since tyrosine is a precursor of both thyroxine and adrenalin, may the presence of the defect in premature infants contribute, under certain conditions, to their instability of body temperature regulation? Is the delicate transparency of the skin of premature infants related to improper utilization of melanin, another product of tyrosine? Does the observed increased excretion of aromatic organic acids in premature infants fed cow's milk play a role in their known tendency to develop severe rickets? If so, this observation may explain, in part at least, the frequently postulated importance of vitamin C in the development of rickets.

Harrer and King<sup>163</sup> studied the effects of deficiency of ascorbic acid on two hydrolytic enzymes and two respiratory enzymes in guinea pigs. As the vitamin was depleted, hepatic esterase activity was observed to decrease progressively to — 65 per cent in cases of acute scurvy. They were unable to obtain any evidence, however, that ascorbic acid is a part of the enzyme, as has been claimed by other authors. There was only a moderate degree of change in the phosphatase activity of the intestinal mucosa and the renal cortex. They demonstrated a marked decrease in the succinic dehydrogenase activity of cardiac and skeletal muscles as scurvy developed but only a moderate decrease in the content of cytochrome oxidase in these muscles.

Fan and Woo<sup>164</sup> administered vitamin C to a patient who had glycogen disease and observed a pronounced increase in the urinary excretion of creatine and creatinine. This effect was not obtained among normal children, because, the authors stated, any increase in the formation of creatine due to ascorbic acid was covered by the normal capacity for storage. The relation of vitamin C metabolism to creatine metabolism is not understood.

Schwachman<sup>165</sup> has carried out some interesting studies on serum phosphatase in 18 cases of infantile scurvy; he found abnormally low values in cases of acute scurvy (average value, 3.2 Bodansky units, as

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163. Harrer, C. J., and King, C. G.: Ascorbic Acid Deficiency and Enzyme Activity in Guinea Pig Tissues, *J. Biol. Chem.* **138**:111-121 (March) 1941.

164. Fan, C., and Woo, T. T.: Effect of Vitamin C on Creatine and Creatinine Metabolism, *Proc. Soc. Exper. Biol. & Med.* **45**:90-92 (Oct.) 1940.

165. Schwachman, H.: Serum Phosphatase in Infantile Scurvy, *J. Pediat.* **19**:38-41 (July) 1941.

compared with a normal mean value of 7.2 Bodansky units), with a substantial increase in serum phosphatase within a week after the beginning of ascorbic acid therapy. As he pointed out, this is to be expected, since previous evidence suggests that bone is the major source of serum phosphatase, and that this enzyme may serve as an index of osteoblastic activity. In rickets the high value for phosphatase in the serum commonly encountered reflects the picture of osteoblastic over-activity, whereas in scurvy the pathologic picture is that of inactivity or inability of the osteoblasts to form a bony matrix.

Recent claims for the value of vitamin C in the treatment of habitual abortion led Israel and Meranze<sup>166</sup> to investigate the effect of ascorbic acid on the endometrium of various animals. They found that the endometrium of the vitamin-treated animals approximated the changes in a progesterone-controlled group.

Basu and Biswas<sup>167</sup> and Basu and Ray<sup>168</sup> presented evidence derived from experiments on human beings which indicates that vitamin C augments muscular contraction, produces quicker relaxation and delays the onset of fatigue. Results of these studies await both experimental and clinical confirmation.

*Metabolism of Vitamin C.*—For a more complete summary of the metabolism of vitamin C, the reader is referred to an excellent review by Farmer.<sup>169</sup> Milhorat, Bartels and Toscani<sup>170</sup> demonstrated that the liver plays an important role in the metabolism of ascorbic acid, since a definite increase in the excretion of this acid followed hepatic injury caused by the inhalation of chloroform. In a subsequent study they and an associate<sup>171</sup> observed that shivering and the administration of epinephrine likewise produced an increased excretion of ascorbic acid in the urine. These observations tend to suggest that the metabolism of vitamin C may be related to that of glycogen. Such a relation would

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166. Israel, S. L., and Meranze, D. R.: Progesterone-Like Effect of Ascorbic Acid (Vitamin C) on the Endometrium, *Endocrinology* **29**:210-214 (Aug.) 1941.

167. Basu, N. M., and Biswas, P.: The Influence of Ascorbic Acid on Contractions and the Incidence of Fatigue on Different Types of Muscles, *Indian J. M. Research* **28**:405-417 (Oct.) 1940.

168. Basu, N. M., and Ray, G. K.: Effect of Vitamin C on the Incidence of Fatigue in Human Muscles, *Indian J. M. Research* **28**:419-426 (Oct.) 1940.

169. Farmer, C. J.: Vitamin C Analysis in Relation to Clinical Problems, *Quart. Bull. Northwestern Univ. M. School* **14**:220-235, 1940.

170. Milhorat, A. T.; Bartels, W. E., and Toscani, V.: Effect of Hepatic Injury on Vitamin C Excretion in Fasting Dogs, *Proc. Soc. Exper. Biol. & Med.* **45**:394-397 (Oct.) 1940.

171. Milhorat, A. T.; Hardy, J. D.; Bartels, W. E., and Toscani, V.: Effect of Shivering, Iodoacetate, and Epinephrine on Vitamin C and Creatine Excretion in Fasting Dogs, *Proc. Soc. Exper. Biol. & Med.* **45**:397-399 (Oct.) 1940.

explain the statement by Ralli and Sherry<sup>172</sup> that the ascorbic acid content both of the blood and of the urine of diabetic dogs was decreased by the administration of insulin, although these investigators have since shown that this effect was caused by a redistribution of ascorbic acid in the elements of the blood.<sup>173</sup>

Ritz, Samuels and Addiss<sup>174</sup> have shown that salicylates and carvone cause an increased excretion of ascorbic acid in the urine of rats. Their results would seem to indicate that whereas salicylates produced this effect through loss from the tissues, carvone brought about an increased production of vitamin C. Drake, Gruber and Haury<sup>175</sup> administered sodium 5,5-diphenylhydantoinate (dilantin sodium) to rats and observed an increased urinary excretion of ascorbic acid accompanied by a diminution in the supply of the acid in the body of the animals.

*Methods Used in the Diagnosis of Deficiency of Ascorbic Acid.*—Results of investigations of the value of determinations of ascorbic acid in the plasma have served to push such determinations into almost total disrepute.<sup>176</sup> So-called scurvy levels (less than 0.4 mg. per hundred cubic centimeters of plasma) are found so commonly among healthy persons that any diagnosis of "subclinical vitamin C deficiency" (a condition of questionable authenticity in any event) based solely on this laboratory procedure rests on uncertain footing. More reliable are determinations of the concentration of ascorbic acid in the whole blood,

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172. Ralli, E. P., and Sherry, S.: Effect of Insulin on Plasma Level and Excretion of Vitamin C, *Proc. Soc. Exper. Biol. & Med.* **43**:669-672 (April) 1940.

173. Ralli, E. P., and Sherry, S.: The Effect of Insulin on the Metabolism of Vitamin C, *Am. J. Physiol.* **133**:p418-p419 (June) 1941.

174. Ritz, N. D.; Samuels, L. T., and Addiss, G.: The Effect of Salicylates and Carvone on the Ascorbic Acid Content of Animal Tissue, *J. Pharmacol. & Exper. Therap.* **70**:362-369 (Dec.) 1940.

175. Drake, M. E.; Gruber, C. M., and Haury, V. G.: Effects of Sodium Diphenyl Hydantoinate (Dilantin) on Vitamin C Level in Tissues and Vitamin C Excretion in Rats, *J. Pharmacol. & Exper. Therap.* **71**:268-272 (March) 1941.

176. Minnich, V.; Wright, S. T.; Moore, C. V., and Spies, T. D.: Whole Blood and Plasma Ascorbic Acid Concentrations in Patients with Pellagra and Associated Deficiency Diseases, *Proc. Soc. Exper. Biol. & Med.* **45**:441-446 (Oct.) 1940. Mindlin, R. L.: Concentration of Ascorbic Acid in the Plasma During the Treatment of Infantile Scurvy, *J. Pediat.* **17**:621-625 (Nov.) 1940. Kastlin, G. J.; King, C. G.; Schlesinger, C. R., and Mitchell, J. W.: Chemical Methods for the Determination of Clinical Vitamin C (Ascorbic Acid) Deficiency, *Am. J. Clin. Path.* **10**:882-893 (Dec.) 1940. Holmes, F. E.; Cullen, G. E., and Nelson, W. E.: Levels of Ascorbic Acid in the Blood Plasma of Apparently Healthy Children, *J. Pediat.* **18**:300-309 (March) 1941. Crane, M. M., and Woods, P. W.: A Study of Vitamin C Nutrition in a Group of School Children: Clinical and Laboratory Studies, *New England J. Med.* **224**:503-509 (March 20) 1941. Milam, D. F., and Wilkins, W.: Plasma Vitamin C Levels in a Group of Children Before and After Dietetic Adjustment, *Am. J. Trop. Med.* **21**:487-491 (May) 1941.

the white cell-platelet fraction or the response of the content of ascorbic acid in the plasma to the parenteral administration of the acid. Even the last method is open to question, since it produces information concerning only the degree of saturation of the organism with the vitamin.

Butler and Cushman have continued their excellent studies of last year, in which they demonstrated that ascorbic acid reaches its highest concentrations in the buffy layer of the blood. They<sup>177</sup> have recently shown that the reducing property of metaphosphoric acid extracts both of leukocytes and of platelets fulfils the chemical criteria for ascorbic acid and that this property appears to depend on some constituent of a not readily diffusible chemical complex. They have further shown that the concentration of this substance depends on the presence of ascorbic acid in the diet and provides an index to deficiency of ascorbic acid which is physiologically significant.

Heinemann<sup>178</sup> has continued his studies on the transference of ascorbic acid from serum to cells and has demonstrated that the partition is not governed by the laws of simple diffusion. Further than this, he has shown<sup>179</sup> that leukocytes in the serum enhance the determination of ascorbic acid, as opposed to erythrocytes, which exert a definite stabilizing effect. There is much greater diffusion of ascorbic acid from serum to leukocytes than to erythrocytes, although Heinemann did not imply that leukocytes do not contain ascorbic acid *in vivo*. Ralli and Sherry<sup>173</sup> have confirmed Heinemann's observations in their work on pancreatectomized dogs. In a previous communication<sup>172</sup> they reported that they had found the administration of insulin to decrease values for ascorbic acid in the plasma; reassessment of this judgment in the light of newer methods has shown this effect to be one of redistribution of the ascorbic acid in the various constituents of the blood.

Those interested in the chemical and the polarographic determination of ascorbic acid will find these subjects well presented by King<sup>180</sup> and Kirk.<sup>181</sup> Ballentine<sup>182</sup> presented a new method for the chemical determination of ascorbic acid in citrus fruit juices.

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177. Butler, A. M., and Cushman, M.: An Ascorbic Acid-Like Reducing Substance in the Buffy Layer of Centrifuged Oxalated Blood, *J. Biol. Chem.* **139**:219-226 (May) 1941.

178. Heinemann, M.: Distribution of Ascorbic Acid Between Cells and Serum of Human Blood, *J. Clin. Investigation* **20**:39-46 (Jan.) 1941.

179. Heinemann, M.: Influences of Erythrocytes and of Leukocytes on Stability and Transfer of Ascorbic Acid in Human Blood, *J. Clin. Investigation* **20**:467-471 (Sept.) 1941.

180. King, C. G.: Chemical Methods for Determination of Vitamin C, *Indust. & Engin. Chem. (Analyt. Ed.)* **13**:225-227 (April 15) 1941.

181. Kirk, M. M.: Polarographic Determination of Ascorbic Acid, *Indust. & Engin. Chem. (Analyt. Ed.)* **13**:625-626 (Sept. 15) 1941.

182. Ballentine, R.: Determination of Ascorbic Acid in Citrus Fruit Juices, *Indust. & Engin. Chem. (Analyt. Ed.)* **13**:89 (Feb. 15) 1941.

*Data on Clinical Use.*—The literature of 1940 seemed to give strong support to the concept that vitamin C has an important role in the healing of wounds. To say that the past year has been a disappointment in this particular respect would constitute an understatement. Save for an excellent piece of experimental work by Hunt,<sup>183</sup> clinical investigators seem to have abandoned a subject which may prove to be of value in the future. Hunt has presented strong support for the theory that ascorbic acid is concerned in the formation of intercellular material. He has shown that this substance appears late and remains in the pre-collagenous state in experimentally produced wounds of subscorbutic guinea pigs, with a resultant loss in tensile strength of the scars. The mature collagen of well healed scars reverted to precollagen when vitamin C was withdrawn from the diet of the animals. In animals deficient in vitamin C there was a tendency toward the formation of hematomas which were not absorbed or organized in the normal manner. Lack of ascorbic acid seemed to delay the absorption of catgut ligatures in experimentally produced wounds. In a single experiment involving a human being there was no difference between the healing of wounds in the presence of deficiency of vitamin C and the healing of wounds in a state of saturation. The period of deprivation, however, was only three months, a period which Crandon, Lund and Dill<sup>184</sup> have shown is insufficient for the production of changes in healing in a previously normal person. Data obtained at necropsy as presented by Hunt are not convincing and need further study. Of 18 patients who died eight or more days after operation, 8 had microscopic changes in their wounds similar to those which occurred in the wounds of subscorbutic guinea pigs. Knowledge of the status of vitamin C nutrition in these particular patients was not sufficient to permit the formation of unreserved conclusions. More significant is the fact that Hunt has been able to reduce the disruption of wounds among his patients by 75 per cent since the preoperative administration of ascorbic acid has become a routine measure. Although he himself criticizes this figure, on the ground that other uncontrolled factors entered into it, it seems noteworthy that in the wounds which failed to heal there was always gross local infection or ischemic necrosis.

Two interesting studies on the relation of vitamin C to the blood-forming organs have appeared during the past year. Liu and his associates<sup>185</sup> divided 6 anemic boys in an institution into two groups,

183. Hunt, A. H.: The Role of Vitamin C in Wound Healing, *Brit. J. Surg.* **28**:436-461 (Jan.) 1941.

184. Crandon, J. H.; Lund, C. C., and Dill, D. B.: Experimental Human Scurvy, *New England J. Med.* **223**:353-369 (Sept. 5) 1940.

185. Liu, S. H.; Chu, H. I.; Yu, T. F.; Hsu, H. C., and Cheng, T. Y.: Anemia in Vitamin C Deficiency and Its Response to Iron, *Proc. Soc. Exper. Biol. & Med.* **46**:603-606 (April) 1941.

administering ascorbic acid to the members of one group and ferrous carbonate to the members of the other. At the end of four weeks it was found that whereas ascorbic acid had raised values for this factor in the plasma to normal, no appreciable changes had occurred in the hemoglobin content, the erythrocyte counts or the hematocrit readings. In contrast to this uniform failure, members of the iron-treated group responded in most cases with a significant increase in these values, despite the persistence of low values for ascorbic acid in the plasma. This agrees with the observations of Lozner<sup>186</sup> and seems to indicate that scorbutic anemia probably is not due to lack of vitamin C itself but is more likely related to a concomitant deficiency of iron.

Stimulated by Barrow's theory that one of the functions of vitamin C is to maintain the concentration of hemoglobin in the blood at a normal value, Deeny<sup>187</sup> administered ascorbic acid and sodium bicarbonate to 2 patients who had polycythemia and reported encouraging results. He was unable to obtain any effect from the administration of ascorbic acid alone.

Cormia<sup>188</sup> and Vail<sup>189</sup> reported that favorable results followed the use of ascorbic acid in diminishing sensitivity to arsenic in antisyphilitic therapy. McDonald and Johnson<sup>190</sup> were unable to establish any relation in guinea pigs between the quantity of ascorbic acid administered parenterally or values for ascorbic acid in the blood and the sensitivity to the repeated intradermal injection of neoarsphenamine.

Goldsmith and associates<sup>191</sup> have presented data to indicate that in the presence of bronchial asthma the requirement of vitamin C is increased. Of 29 patients, subnormal values for ascorbic acid in the plasma were observed in 19, and it was found to be more difficult to maintain values for ascorbic acid in the blood of patients who had bronchial asthma. In 2 patients there seemed to be reverse parallelism between the level of ascorbic acid in the blood and the frequency and

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186. Lozner, E. L.: Studies on Hemoglobin Regeneration in Patients with Vitamin C Deficiency, *New England J. Med.* **224**:265-268 (Feb. 13) 1941.

187. Deeny, J.: Polycythemia and Vitamin C, *Brit. M. J.* **2**:864-866 (Dec. 21) 1940.

188. Cormia, F. E.: Postarsphenamine Dermatitis: The Relation of Vitamin C to the Production of Arsphenamine Sensitiveness, and Its Use as an Adjunct to Further Arsphenamine Therapy in Patients with Cutaneous Hypersensitiveness to the Arsphenamines, *J. Invest. Dermat.* **4**:81-93 (Feb.) 1941.

189. Vail, A. D.: Influence of Vitamin C Therapy on Arsenical Sensitivity, *J. Missouri State M. A.* **38**:110-120 (April) 1941.

190. McDonald, F. M., and Johnson, H. H.: Ascorbic Acid and Arsphenamine Dermatitis: An Experimental Study, *Arch. Dermat. & Syph.* **43**:682-688 (April) 1941.

191. Goldsmith, G. A.; Ogaard, A. T., and Gowe, D. F.: Vitamin C (Ascorbic Acid) Nutrition in Bronchial Asthma: An Estimation of the Daily Requirement of Ascorbic Acid, *Arch. Int. Med.* **67**:597-608 (March) 1941.

severity of the attacks. Any beneficial effect obtained was probably nonspecific, however, since 5 other patients were not benefited by administration of the vitamin.

Ludden, Flexner and Wright<sup>192</sup> conducted careful studies on the absorption of vitamin C by patients who had gastrointestinal disturbances. They were unable to demonstrate interference with such absorption in the presence of gastric lesions, since ascorbic acid seems to be absorbed in the intestinal tract. The authors stated that they plan to report a case in which the entire jejunum and all but the terminal 6 to 8 inches (15 to 20 cm.) of ileum were resected; it was necessary for the patient to receive 35 Gm. of ascorbic acid before the value for the vitamin in the plasma could be increased to 0.7 mg. per hundred cubic centimeters, and for maintenance of such a value a daily dose of 700 mg. per hundred cubic centimeters was required. Three patients requiring increased maintenance doses were suffering from hypermotility of the gastrointestinal tract. Contrary to an accepted belief, achlorhydria and alkali therapy failed to interfere with absorption.

Marchmont-Robinson<sup>193</sup> conducted a survey on the effects of the administration of vitamin C to lead workers. Carefully controlled studies of basophilic aggregation counts, urinary excretion of lead and subjective symptoms seemed to indicate that a beneficial effect of some extent proceeds from such therapy. He could find no evidence that ascorbic acid promotes the storage of lead; rather, he suggested that the reverse is true. His conclusion, however, that the absorption of lead produces avitaminosis C and that the symptoms of chronic lead poisoning are due to subclinical scurvy seems hardly justifiable.

During the past year favorable reports have appeared on the use of vitamin C in cases of radiation sickness,<sup>92</sup> gingivitis,<sup>194</sup> inflammatory corneal conditions<sup>195</sup> and pain in the temporomandibular region.<sup>196</sup>

Hofmeyr<sup>197</sup> made a rather extensive study of ascorbic acid metabolism among the Negroes of South Africa and reviewed the importance

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192. Ludden, J. B.; Flexner, J., and Wright, I. S.: Studies on Ascorbic Acid Deficiency in Gastric Diseases: Incidence, Diagnosis and Treatment, *Am. J. Digest. Dis.* **8**:249-252 (July) 1941.

193. Marchmont-Robinson, S. W.: Effect of Vitamin C on Workers Exposed to Lead Dust, *J. Lab. & Clin. Med.* **26**:1478-1481 (June) 1941.

194. Campbell, H. G., and Cook, R. P.: Treatment of Gingivitis with Ascorbic Acid, *Brit. M. J.* **1**:360-361 (March 8) 1941.

195. Lyle, T. K., and McLean, D. W.: Vitamin "C" (Ascorbic Acid)—Its Therapeutic Value in Inflammatory Conditions of the Cornea, *Brit. J. Ophth.* **25**:286-295 (June) 1941.

196. Sinclair, J. A.: Vitamin C Deficiency: A Factor in Producing Subluxation, Pain in the Temporomandibular Area and Other Dental Involvements, *Dental Items Interest* **63**:313-317 (April) 1941.

197. Hofmeyr, H. O.: Unpublished data.

which ascorbic acid nutrition played in the early establishment of civilization in this part of Africa.

*Human Requirements and Sources.*—Hathaway and Meyer<sup>198</sup> found the marginal level of the daily intake of ascorbic acid in 4 children of preschool age to be 30 mg. Goldsmith, Ogaard and Gowe<sup>199</sup> administered 50 mg. of ascorbic acid daily to 12 ambulatory patients and found that this amount was sufficient to maintain a value for ascorbic acid in the blood of 1 mg. per hundred cubic centimeters for seven to eighteen weeks. These, however, are isolated figures, and the recommended allowance for this vitamin was set at higher values than these by the Committee on Food and Nutrition of the National Research Council (see table).

Holmes, Pigott and Tripp<sup>200</sup> conducted an interesting study on the relative costs of various sources of vitamin C and found canned orange juice, canned grapefruit juice, fresh orange juice and fresh grapefruit juice to be the cheapest, in the order named. Other interesting and valuable studies on sources of vitamin C are listed here.<sup>201</sup>

#### VITAMIN D

*Chemical and Physiologic Properties.*—It has been recognized for many years that vitamin D probably exerts its antirachitic properties through its ability to increase the concentration of phosphate in the serum. Previous studies have shown that this elevation is effected by increase in the intestinal absorption and diminution in the urinary excretion of phosphates. Harrison and Harrison<sup>202</sup> recently have investigated this urinary excretion of phosphates in dogs and have been able to show that in rachitic dogs there is a diminution in tubular reabsorption. After the administration of vitamin D they observed a rapid increase in this reabsorption, the rate of glomerular filtration remaining unchanged. These observations suggest that refractory rickets may have a basis in

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198. Hathaway, M. L., and Meyer, F. L.: Studies on the Vitamin C Metabolism of Four Preschool Children, *J. Nutrition* **21**:503-514 (May) 1941.

199. Goldsmith, G. A.; Ogaard, A. T., and Gowe, D. F.: Estimation of the Ascorbic Acid (Vitamin C) Requirement of Ambulatory Patients, *Arch. Int. Med.* **67**:590-596 (March) 1941.

200. Holmes, A. D.; Pigott, M. G., and Tripp, F.: Comparative Costs of Vitamin C in Fresh and Commercially Canned Fruit and Vegetable Juices, *New England J. Med.* **225**:68-73 (July 10) 1941.

201. Keller, M. L., and Minot, A. S.: "Pot Liquor": A Neglected Source of Vitamin C for the Feeding of Infants, *South. M. J.* **34**:163-164 (Feb.) 1941. Vitamin C for the Baby, Annotations, *Lancet* **1**:48 (Jan. 11) 1941. Chappell, G.: The Distribution of Vitamin C in Foods Sold on the Open Market, *J. Hyg.* **40**:699-732 (Dec.) 1940.

202. Harrison, H. E., and Harrison, H. C.: The Renal Excretion of Inorganic Phosphate in Relation to the Action of Vitamin D and Parathyroid Hormone, *J. Clin. Investigation* **20**:47-55 (Jan.) 1941.



permanently damaged tubular epithelium, which will no longer respond to stimulation by vitamin D. The effect of parathyroid extract in lowering the serum phosphate was shown to occur by means of diminution of the tubular reabsorption of this ion.

That the bony changes in rickets are merely consequences of disturbances in the calcium and phosphorus of the serum has been assumed in the past. Kraemer and his associates<sup>203</sup> have presented evidence that this may not be entirely the case. In a preliminary report of results of studies in vitro on the bones of rachitic and nonrachitic rats, they have shown that vitamin D seems to exert some type of direct effect on bone. Bones of deficient animals did not take up calcium and phosphorus salts from incubation solutions as rapidly as did normal bones and gave up more of these bone-forming salts into solutions containing none of these ions. These observations may lead to revolutionary changes in the present concept of the pathologic physiology of rickets.

Shohl and Farber<sup>204</sup> studied the effect of dihydrotachysterol in high calcium, low phosphorus rickets of rats. Although they were able to effect a cure by administration of this compound, they found vitamin D to be four hundred times as effective and only a fifth as toxic. They observed that dihydrotachysterol resembles vitamin D in its action and differs from parathyroid in that it increases calcium absorption and diminishes the urinary excretion of phosphate. These observations agree with the hypothesis presented in 1938 by Albright and associates.<sup>205</sup>

The reader will find an excellent summary of the subject of calcium and phosphorus metabolism and its relation to vitamin D and the parathyroid glands in a recent paper by Leverton.<sup>206</sup>

Opper<sup>207</sup> demonstrated by means of experimentation with animals that renal damage is an important factor in the production of toxicity arising from overdosage with vitamin D. His most significant observation was a high value for phosphate in the serum, there being little variation in values for serum calcium among normal control animals.

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203. Kraemer, V. V.; Landtman, B., and Simola, P. E.: In Vitro Studies on the Role of Vitamin D in the Metabolism of Calcium and Phosphorus in the Rat Bones, *Acta physiol. Scandinav.* **1**:285-298, 1940.

204. Shohl, A. T., and Farber, S.: Effect of A. T. 10 (Dihydrotachysterol) on Rickets in Rats Produced by High-Calcium-Low-Phosphorus Diets, *J. Nutrition* **21**:147-154 (Feb.) 1941.

205. Albright, F.; Bloomberg, E.; Drake, T., and Sulkowitch, H. W.: A Comparison of the Effects of A. T. 10 (Dihydrotachysterol) and Vitamin D on Calcium and Phosphorus Metabolism in Hypoparathyroidism, *J. Clin. Investigation* **17**:317-329 (May) 1938.

206. Leverton, W. R.: Parathormone and Vitamin D: Calcium and Phosphorus Metabolism, *M. Bull. Vet. Admin.* **17**:266-273 (Jan.) 1941.

207. Opper, L.: Effect of Renal Damage on the Toxicity of Hypervitaminosis D in Rats, *Arch. Path.* **31**:569-577 (May) 1941.

This observation is of importance when it is recalled that one of the earliest signs of renal insufficiency is elevation of the value for serum phosphorus.

New methods for the assay of vitamin D continue to appear,<sup>208</sup> and Milas, Heggie and Raynolds<sup>209</sup> have presented a good summary of previous work, with detailed procedures.

*Clinical Use.*—Readers interested in the subject of vitamin D therapy will find Kramer's<sup>210</sup> paper a complete survey. The past year has not been particularly productive in the field of clinical investigation. Liu and his associates<sup>211</sup> have continued their fine work along this line. In a study of female patients who had osteomalacia they were unable to find any inherent inability of these patients to retain minerals during pregnancy. They proved conclusively that in the absence of adequate supplies of calcium and vitamin D pregnancy and lactation are important factors in demineralization of the skeleton. They expressed the opinion that of these two substances vitamin D is probably the more important, provided that there is a reasonable intake of calcium.

Vollmer<sup>212</sup> reported observations made at necropsy concerning a 3 year old child who had received crystalline vitamin D<sub>3</sub> (2,260,000 U. S. P. units of vitamin D) within twenty-six days of its death. Detailed study did not reveal any changes which could be ascribed to hypervitaminosis D. Similar negative observations were made concerning a child who received an equivalent of 1,260,000 units of vitamin D within nine days before death. Bioassay failed to reveal any vitamin D in the brains of these patients, in contradiction to the results of Windorfer, who found that 4 per cent of the vitamin D that had been administered was present in the brain.

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208. Martin, G. J.: The Use of Osteotropic Dyes in a Modified Line Test for Vitamin D, *J. Lab. & Clin. Med.* **26**:714-719 (Jan.) 1941. Loy, H. W., Jr.; DeWitt, J. B., and Knudsen, L. F.: Observations on the Chick Method for the Assay of Vitamin D: I. Relative Accuracy of Group and Individual Ashing Procedures and Relation of Chick Weight to Per Cent Bone Ash, *J. A. Offic. Agric. Chemists* **24**:190-196 (Feb.) 1941.

209. Milas, N. A.; Heggie, R., and Raynolds, J. A.: A Spectroscopic Method for the Quantitative Estimation of Vitamin D, *Indust. & Engin. Chem. (Analyt. Ed.)* **13**:227-231 (April 15) 1941.

210. Kramer, B.: Vitamin D Therapy, *J. Mt. Sinai Hosp.* **8**:188-209 (Sept.-Oct.) 1941.

211. Liu, S. H.; Chu, H. I.; Hsu, H. C.; Chao, H. C., and Cheu, S. H.: Calcium and Phosphorus Metabolism in Osteomalacia: XI. The Pathogenetic Role of Pregnancy and Relative Importance of Calcium and Vitamin D Supply, *J. Clin. Investigation* **20**:255-271 (May) 1941.

212. Vollmer, H.: Distribution of Vitamin D in the Brain After Repeated Administration of Massive Doses: Histologic Investigation of D-Hypervitaminosis, *Arch. Pediat.* **58**:9-20 (Jan.) 1941.

Wagner and Jones<sup>213</sup> applied viosterol in oil to the skin of a small group of infants and demonstrated roentgenographic evidence of healing rickets. The amounts required were much greater than those customarily employed in oral administration, and the authors did not recommend routine administration of viosterol in such a manner. They stated that it may serve as a route of administration to patients who exhibit defects in gastrointestinal absorption.

Two reports on the use of vitamin D in psoriasis have appeared; Krafka<sup>214</sup> claimed good results, and Wright<sup>215</sup> expressed the opinion that vitamin D is not specific for this disease and that it may give rise to reactions.

#### VITAMIN E

*Chemical and Physiologic Properties.*—Although there has been assembled a large amount of data on this subject, investigations of the chemical aspects of vitamin E and investigations involving experimentation with animals have not been particularly fruitful. Several articles in which the chemistry of the tocopherols were discussed are listed here.<sup>216</sup>

Friedman and Mattill<sup>217</sup> studied the consumption of oxygen by the skeletal muscles of vitamin E-deficient rats and found it was as high as 40 per cent above normal in young animals without dystrophy and slightly elevated in older rats with dystrophy. The administration of

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213. Wagner, E. A., and Jones, D. V.: Observations on the Application of Vitamin D to the Skin, *Ohio State M. J.* **37**:249-254 (March) 1941.

214. Krafka, J.: Vitamin D Therapy in Psoriasis, *J. M. A. Georgia* **30**:398-400 (Sept.) 1941.

215. Wright, C. S.: Vitamin D Therapy in Dermatology, *Arch. Dermat. & Syph.* **43**:145-154 (Jan.) 1941.

216. Ridgway, R. R.; Drummond, J. C., and Wright, M. D.: The Biological Activity of the Oxidation Products of  $\alpha$ -Tocopherol, *Biochem. J.* **34**:1569-1573, 1940. Smith, L. I.; Wawzonek, S., and Miller, H. C.: The Chemistry of Vitamin E: XXVI. 5-Hydroxy-4, 6, 7-Trimethylcoumaran, 5-Hydroxy-2, 2, 4, 6, 7-Pentamethylcoumaran, 6-Hydroxy-2, 2, 5-Trimethyl-7, 8-Benzochroman, and 5-Hydroxy-2, 4-Dimethyl-6, 7-Benzocoumaron, *J. Organic Chem.* **6**:229-235 (March) 1941. Smith, L. I.; Ruoff, P. M., and Wawzonek, S.: The Chemistry of Vitamin E: XXVII. Oxidation of Hydroquinones, *p*-Hydroxychromans and *p*-Hydroxycoumarans to Quinones with Ceric Sulfate, *ibid.* **6**:236-241 (March) 1941. Smith, L. I., and Opie, J. W.: The Chemistry of Vitamin E: XXVIII. (1) Synthesis of the Three Dimethylethylquinones, *ibid.* **6**:427-436 (May) 1941. Smith, L. I.; Kolthoff, I. M.; Wawzonek, S., and Ruoff, P. M.: The Chemistry of Vitamin E: XXIX. Studies of the Behavior of Compounds Related to Vitamin E at the Dropping Mercury Electrode, *J. Am. Chem. Soc.* **63**:1018-1024 (April) 1941. Tishler, M., and Evans, H. M.: Vitamin E Activities of Some Compounds Related to  $\alpha$ -Tocopherol, *J. Biol. Chem.* **139**:241-245 (May) 1941.

217. Friedman, I., and Mattill, H. A.: The Oxygen Consumption of Skeletal Muscle from Animals Deprived of Vitamin E, *Am. J. Physiol.* **131**:595-600 (Jan.) 1941.

alpha tocopherol lowered this consumption within twenty-four hours. These authors recalled the suggestion of Szent-Györgyi that there exists in animal tissues a series of biocatalysts which accomplish the gradual degradation of a metabolite to such an extent that its total energy is released stepwise, rather than completely at a single bound. They then postulated that in the absence of tocopherol one of the intermediate and delaying steps may drop out, with the result that oxidation proceeds more rapidly. Support is lent to this theory if it is recalled that results of in vitro experiments have shown alpha tocopherol to possess anti-oxidation properties.

Krakower and Axtmayer <sup>218</sup> have shown that certain muscular lesions in rats formerly thought to be related to avitaminosis A actually are results of deficiency of tocopherol. Beard and Pizzolato <sup>219</sup> were able to increase the creatine content of the muscles of rats by 20 to 36 per cent by means of the administration of vitamin B<sub>6</sub>, nicotinic acid and vitamin E and concluded that these substances must be considered as necessary for normal muscle metabolism. Holmes and Pigott <sup>220</sup> produced definite improvement in vitamin E-deficient rats which had muscular dystrophy by the administration of thiamine hydrochloride. Mackenzie and McCollum <sup>221</sup> demonstrated the skeletal muscles of the male rabbit to be more sensitive to deficiency of vitamin E than the testes, in contrast to the opposite reaction in rats.

Biddulph and Meyer <sup>222</sup> studied the effect of deprivation of vitamin E on the endocrine glands of rats, with no impressive results. The usual testicular degeneration appeared, but there was no effect on ovarian size or function. The thyroid glands of male rats increased as much as 100 per cent, but there were no striking changes in any other glands. Beerstecher <sup>223</sup> studied the estrogens excreted in the urine of vitamin E-deficient female rats and found their values to decrease abruptly at about

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218. Krakower, C., and Axtmayer, J. H.: Effect of Alpha-Tocopherol on Lesions of Skeletal Muscles in Rats on Vitamin A-Deficient Diets, *Proc. Soc. Exper. Biol. & Med.* **45**:583-586 (Nov.) 1940.

219. Beard, H. H., and Pizzolato, P.: The Effect of Parenteral Injection of Crystalline Vitamins upon the Concentration of Muscle Creatine in the Rat, *J. Am. Dietet. A.* **17**:446-449 (May) 1941.

220. Holmes, A. D., and Pigott, M. G.: The Effect of Thiamin Hydrochloride on the Muscular Dystrophy of Avitaminosis-E, *Am. J. Physiol.* **132**:211-214 (Feb.) 1941.

221. Mackenzie, C. G., and McCollum, E. V.: Muscular Dystrophy in the Absence of Testicular Degeneration in Vitamin E Deficiency, *Proc. Soc. Exper. Biol. & Med.* **47**:148-152 (May) 1941.

222. Biddulph, C., and Meyer, R. K.: The Influence of Vitamin E-Deficiency on the Endocrine Glands of Rats, Particularly on the Gonadotropic Hormone Content of the Pituitary Gland, *Am. J. Physiol.* **132**:259-271 (Feb.) 1941.

223. Beerstecher, E., Jr.: Estrogens in Urine of Normal and Vitamin E Depleted Rats, *Endocrinology* **28**:344 (Feb.) 1941.

the eighteenth day of deprivation. He found a rather significant correlation between the decrease in estrogens and the decrease in weight of the resorbing fetuses. Adamstone<sup>224</sup> found that vitamin E hastened the effect of testosterone propionate in reviving the secondary sex characteristics of caponized male fowls and concluded that a certain quantity of vitamin E in the diet is necessary for the most effective utilization of androgens.

Mackenzie, Mackenzie and McCollum<sup>225</sup> observed that the administration of cod liver oil rendered alpha tocopherol ineffective in the prevention of muscular dystrophy in rabbits. The cause of this is obscure, but the authors have offered three possible explanations: 1. Vitamin E may be destroyed by cod liver oil after ingestion. 2. Cod liver oil may exert some sort of toxic action on the muscles. 3. The destructive action of cod liver oil may be prevented by vitamin E, by virtue of its activity as either a vitamin or an antioxidant.

Adamstone<sup>226</sup> fed chicks on ferric chloride-treated rations supplemented by halibut liver oil and observed the development of a type of anemia characterized by marked erythrophagocytosis. When the halibut liver oil was replaced by cod or salmon liver oil, this reaction did not appear; it was likewise prevented by the addition of vitamin E to the diet. The cause of this phenomenon is not clear, but it is suggested that treatment of the food destroyed some substance essential to the erythrocytes, a substance which may be available in cod and salmon liver oils.

*Clinical Use.*—The various claims and counterclaims for the use of vitamin E in neuromyogenic disturbances are at such variance as to make critical analysis almost impossible. Save for the studies of Wechsler,<sup>227</sup> favorable reports<sup>228</sup> have been based on small series of

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224. Adamstone, F. B.: Relation of Vitamin E to the Effectiveness of Testosterone Injected into Caponized Male Fowls, *Arch. Path.* **31**:706-710 (June) 1941.

225. Mackenzie, C. G.; Mackenzie, J. B., and McCollum, E. V.: Uncomplicated Vitamin E Deficiency in the Rabbit and Its Relation to the Toxicity of Cod Liver Oil, *J. Nutrition* **21**:225-234 (March) 1941.

226. Adamstone, F. B.: Erythrophagocytosis in Chicks Reared on a Vitamin E-Deficient Ration Supplemented with Halibut Liver Oil, *Arch. Path.* **31**:613-621 (May) 1941.

227. Wechsler, I. S.: The Treatment of Amyotrophic Lateral Sclerosis with Vitamin E (Tocopherols), *Am. J. M. Sc.* **200**:765-778 (Dec.) 1940.

228. Weinberg, M. H., and Knoll, A. F.: Beneficial Effect of Vitamin E on Amyotrophic Lateral Sclerosis Syndrome: Report of a Case in Which This Syndrome Was Precipitated by Sulfathiazole, *M. Rec.* **152**:447-448 (Dec. 18) 1940. Stone, S.: Vitamin E in the Treatment of Muscle Disorders of Infancy and Childhood, *J. Pediat.* **18**:310-316 (March) 1941. Slaughter, R. F., and Cleckley, H.: The Treatment of Intrinsic Cord Disease with Vitamin E, *J. M. A. Georgia* **30**:106-108 (March) 1941. de Gutiérrez-Mahoney, W.: Neural Myatophy and Vitamin E, *South. M. J.* **34**:389-394 (April) 1941.

cases, in which there was little chance for adequate control. In discussing a paper by Rhoads,<sup>229</sup> Stone stated that he observed improvement in 10 of 20 patients who had muscular dystrophy and were treated with vitamin E. This again is at variance with Wechsler's<sup>227</sup> observations, since Wechsler was unable to note any improvement in this type of disturbance after administration of the vitamin. It is difficult to reconcile these reports with those of Doyle and Merritt,<sup>230</sup> as well as with those of other investigators,<sup>231</sup> who were unable to observe any objective improvement among patients in relatively large series of cases. Fleischmann<sup>232</sup> treated 3 patients with alpha tocopherol, with completely negative results and with no effect on the creatine-creatinine excretion. The latter observation led him to believe that there is some fundamental difference between the neuromyopathies of human beings and those of vitamin E-deficient animals. On the basis of determinations of serum tocopherol Wechsler and associates<sup>233</sup> could not discover any difference in values obtained for their patients and those of normal controls (0.59 to 1.62 mg. per hundred cubic centimeters). After the administration of tocopherol, there was a uniform increase in these values, but there was no relation between this increase and the clinical improvement. These observations led them to conclude that these "figures . . . do not point to a simple deficiency in amyotrophic lateral sclerosis." A good summary of this entire subject has appeared in editorial form in the *Lancet*.<sup>234</sup>

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229. Rhoads, C. P.: Deficiency Diseases: Their Diagnosis and Treatment, *New England J. Med.* **224**:493-497 (March 20) 1941.

230. Doyle, A. M., and Merritt, H. H.: Vitamin Therapy of Diseases of Neuromuscular Apparatus, *Arch. Neurol. & Psychiat.* **45**:672-679 (April) 1941.

231. McBryde, A., and Baker, L. D.: Vitamin Therapy in Progressive Muscular Dystrophy: Vitamin B<sub>6</sub>, Other Factors of the B Complex, and Vitamin E, *J. Pediat.* **18**:727-731 (June) 1941. Worster-Drought, C., and Shafar, J.: Motor Neuron Degeneration Treated with Vitamin E, *Lancet* **2**:209-212 (Aug. 23) 1941. Harris, M. M.: Negative Therapeutic and Metabolic Effects of Synthetic Alpha-Tocopherol (Vitamin E) in Muscular Dystrophy, *Am. J. M. Sc.* **202**:258-264 (Aug.) 1941. Ferrebee, J. W.; Klingman, W. O., and Frantz, A. M.: Vitamin E and B<sub>6</sub>: Clinical Experience in the Treatment of Muscular Dystrophy and Amyotrophic Lateral Sclerosis, *J. A. M. A.* **116**:1895-1896 (April 26) 1941. Denker, P. G., and Scheinman, L.: Treatment of Amyotrophic Lateral Sclerosis with Vitamin E (Alpha-Tocopherol), *ibid.* **116**:1893-1895 (April 26) 1941. Fitzgerald, G., and McArdle, B.: Vitamins E and B<sub>6</sub> in the Treatment of Muscular Dystrophy and Motor Neurone Disease, *Brain* **64**:19-42 (March) 1941.

232. Fleischmann, W.: Creatine-Creatinine Excretion in Neuromuscular Diseases Treated with Alpha-Tocopherol and with Testosterone, *Proc. Soc. Exper. Biol. & Med.* **46**:94-97 (Jan.) 1941.

233. Wechsler, I. S.; Mayer, G. G., and Sobotka, H.: Tocopherol Level in Serum of Normals and Patients with Amyotrophic Lateral Sclerosis, *Proc. Soc. Exper. Biol. & Med.* **47**:152-156 (May) 1941.

234. Vitamin E Falls from Grace, editorial, *Lancet* **2**:219-220 (Aug. 23) 1941.

Lubin and Waltman<sup>235</sup> published results of a study of the role of vitamin E in habitual abortion. Among their 7 patients the administration of alpha tocopherol was followed by successful parturition in 5. The authors were properly conservative in their conclusions but expressed the belief that their results were sufficiently encouraging to stimulate further investigation. Adamstone<sup>236</sup> observed a disturbance of cholesterol metabolism in vitamin E-deficient chicks; since there may be a similar disturbance in cases of habitual abortion, he suggested that there may be a definite role for vitamin E in cholesterol metabolism.

#### VITAMIN K

*Chemical and Physiologic Properties.*—The compound 2-methyl-1,4-naphthoquinone is one of the most active synthetic antihemorrhagic compounds known. Because of the wide usefulness of this compound in clinical medicine, the Council on Pharmacy and Chemistry of the American Medical Association,<sup>237</sup> on the recommendation of the Committee on Nomenclature, authorized "menadione" as the nonproprietary name for this substance.

Many of the advances in the chemistry of vitamin K have been made in the study of various quinone derivatives,<sup>238</sup> and excellent reviews<sup>239</sup> of these investigations have appeared. Naturally, considerable effort also has been made in the hope of obtaining knowledge concerning the activity and structure of vitamin K. Fieser and his associates<sup>240</sup> studied some seventy-nine compounds with antihemorrhagic activity in an effort to obtain some knowledge on this point. They found that antihemor-

235. Lubin, S., and Waltman, R.: The Use of Synthetic Vitamin E in the Treatment of Abortion, *Am. J. Obst. & Gynec.* **41**:960-970 (June) 1941.

236. Adamstone, F. B.: Cholesterol Content of Brain in Nutritional Encephalomalacia of Vitamin E-Deficient Chicks, *Arch. Path.* **31**:711-716 (June) 1941.

237. Menadione, Nonproprietary Term for the Substance 2-Methyl-1, 4-Naphthoquinone, report of the Council on Pharmacy and Chemistry, *J. A. M. A.* **116**:1054 (March 15) 1941.

238. (a) Lee, J.; Solmssen, U. V.; Steyermark, A., and Foster, R. H. K.: Antihemorrhagic Activity of Tetra Sodium 2-Methyl-1, 4-Naphthohydroquinone Diphosphoric Acid Ester and Other Naphthoquinone Derivatives, *Proc. Soc. Exper. Biol. & Med.* **45**:407-412 (Oct.) 1940. (b) Foster, R. H. K., with the technical assistance of Clark, H. H.: Pharmacological Observations on Tetra-Sodium-2-Methyl-1, 4-Naphthohydroquinone Diphosphoric Acid Ester, *ibid.* **45**:412-415 (Oct.) 1940. (c) Almquist, H. J., and Klose, A. A.: Comparative Activities of Certain Antihemorrhagic Compounds, *ibid.* **45**:55-59 (Oct.) 1940. (d) Martin, G. J., and Lischer, C. F.: Polyhydroxyanthraquinones Affecting Coagulation Time in Vitamin K Deficiency, *J. Biol. Chem.* **137**:169-171 (Jan.) 1941.

239. Karrer, P.: Das antihämorrhagische Vitamin K, *Schweiz. med. Wchnschr.* **70**:537-541 (June 15) 1940. Doisy, E. A.; Binkley, S. B., and Thayer, S. A.: Vitamin K, *Chem. Rev.* **28**:477-517 (June) 1941.

240. Fieser, L. F.; Tishler, M., and Sampson, W. L.: Vitamin K Activity and Structure, *J. Biol. Chem.* **137**:659-692 (Feb.) 1941.

rhagic activity of any biologically significant magnitude is found only in the 1,4-naphthoquinone series or among compounds which are convertible into such quinones. Considerable specificity is evident in the series which embraces vitamin K<sub>1</sub> and vitamin K<sub>2</sub>. These investigators reported that the high potency of menadione is almost completely wiped out when the methyl group is replaced by an ethyl or a propyl group or when a methyl group is introduced at any of the four positions in the benzenoid ring. It is interesting that the antihemorrhagic activity which was observed in a considerable number of the compounds tested by these authors seemed to be attributable not to the function of the actual substance administered but to its conversion in the animal body to a vitamin K type principle in the course of the action. McCawley and Gurchot<sup>241</sup> reported that the degree of activity of vitamin K is roughly proportional to the length of the side chain and to the degree to which it approximates the characteristic structure of natural vitamins. This group of authors believed that vitamin K is a reversible oxidation-reduction catalyst, the hydroquinone form of which is readily oxidized by molecular oxygen. It is suggested that the reversible character of the vitamin may be used to explain the fact that small quantities are effective clinically.

Javert and Macri<sup>242</sup> emphasized that excessive amounts of mineral oil administered with meals may prevent proper absorption of vitamin K, with a resulting deficiency of prothrombin in the circulating blood. Morse and Schmidt<sup>243</sup> pointed out that both phthiocol (2-methyl-3-hydroxy-1,4-naphthoquinone) and menadione are absorbed from the intestinal tracts of rats with bile fistulas and that desoxycholic acid is not necessary to insure the absorption of these compounds. It has been reported that a synthetic compound possessing vitamin K activity produces vitamin K stores in newly hatched chicks when injected into eggs prior to incubation. The injected vitamin apparently protects against the rapid and extreme decrease in prothrombin which occurs when chicks are placed on a vitamin K-free diet.<sup>244</sup> McElroy and Goss<sup>245</sup> have demonstrated that vitamin K is not a dietary essential for

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241. McCawley, E. L., and Gurchot, C.: A Mechanism of Action for Vitamin K, Univ. California Publ., Pharmacol. **1**:325-338, 1940.

242. Javert, C. T., and Macri, C.: Prothrombin Concentration and Mineral Oil, Am. J. Obst. & Gynec. **42**:409-414 (Sept.) 1941.

243. Morse, L. M., and Schmidt, C. L. A.: Absorption of 2-Methyl-1, 4-Naphthoquinone Phthiocol by Bile Fistula Rats, Proc. Soc. Exper. Biol. & Med. **46**:415-416 (March) 1941.

244. Tidrick, R. T.; Stamler, F. W.; Joyce, F. T., and Warner, E. D.: Vitamin K Storage and Prothrombin Levels in Chicks Obtained from Injected Eggs, Proc. Soc. Exper. Biol. & Med. **47**:438-440 (June) 1941.

245. McElroy, L. W., and Goss, H.: A Quantitative Study of Vitamins in the Rumen Contents of Sheep and Cows Fed Vitamin-Low Diets: I. Riboflavin and Vitamin K, J. Nutrition **20**:527-540 (Dec.) 1940.



the cow and that the rumen of the experimental animal is a good source of vitamin K. It has also been found <sup>246</sup> that vitamin K and antihemorrhagic compounds in general are effective in promoting the growth of certain bacteria. Almquist and Mecchi <sup>247</sup> observed that menadione, pure vitamin K<sub>1</sub> and other quinone derivatives do not prevent erosion of the lining of the gizzard of chicks.

In reasonable clinical doses no serious untoward reaction has yet been observed among human beings after the administration of either natural or synthetic compounds possessing vitamin K activity. Toxic effects have been noted among animals, however.<sup>248</sup> Shimkin,<sup>248a</sup> in a study of the acute and chronic toxic effects of six naphthoquinone compounds of vitamin K activity, observed that the compounds in high doses are respiratory depressants and produce acute vascular congestion which is sufficient to cause hemorrhagic extravasation into the renal tubules and within the liver. Loss of weight, anemia or morphologic changes were not observed in mice which were given subcutaneous injections of 4 to 18 mg. of menadione daily for three to six weeks.

The wide interest in vitamin K and the associated naphthoquinones has given rise to the need for convenient and accurate methods for their estimation. A step in this direction was made by Trenner and Bacher,<sup>249</sup> who described a method by which many quinone-like substances may be assayed. It is a quantitative reduction-oxidation method. They encountered no interference when other fat-soluble vitamins, such as A, B or E, were used. Excellent critical reviews of biologic methods for measuring vitamin K were given by Ansbacher <sup>250</sup> and Almquist.<sup>251</sup>

*Prothrombin.*—Recently, a method has been described <sup>252</sup> by which prothrombin can be produced in a fairly pure form, and in several other

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246. Woolley, D. W., and McCarter, J. R.: Antihemorrhagic Compounds as Growth Factors for Johne's Bacillus, *Proc. Soc. Exper. Biol. & Med.* **45**:357-360 (Oct.) 1940.

247. Almquist, H. J., and Mecchi, E.: Influence of Bile Acids, Vitamin K and Cinchophen on Erosions of the Chick Gizzard Lining, *Proc. Soc. Exper. Biol. & Med.* **46**:168-172 (Jan.) 1941.

248. (a) Shimkin, M. B.: Toxicity of Naphthoquinones with Vitamin K Activity in Mice, *J. Pharmacol. & Exper. Therap.* **71**:210-214 (March) 1941.  
(b) Foster.<sup>238b</sup>

249. Trenner, N. R., and Bacher, F. A.: A Quantitative Reduction-Oxidation Method for the Estimation of Vitamin K<sub>1</sub> and Associated Quinones and Naphthoquinones, *J. Biol. Chem.* **137**:745-755 (Feb.) 1941.

250. Ansbacher, S.: The Bioassay of Vitamin K, *J. Nutrition* **21**:1-12 (Jan.) 1941.

251. Almquist, H. J.: Vitamin K, *Physiol. Rev.* **21**:194-216 (Jan.) 1941.

252. Seegers, W. H., and Smith, H. P.: The Purification of Prothrombin, *J. Biol. Chem.* **140**:677-678 (Aug.) 1941.

studies<sup>253</sup> the physical and physiologic properties of this substance have been considered. It has been suggested,<sup>254</sup> also, that prothrombin is destroyed in the lung. These data have not yet been confirmed. Cullen and his associates<sup>255</sup> found that chloroform anesthesia in the human being produces a decrease in the plasma prothrombin level, whereas ether and cyclopropane anesthesia do not. They assumed that the decrease in the level of plasma prothrombin which occurs after surgical operation on patients suffering from obstructive jaundice or biliary fistula evidently is due essentially to factors other than the anesthetic agent itself.

Methods for the measurement of prothrombin now in general use are those described by Quick and his associates and by Warner and his co-workers. Herbert<sup>256</sup> described a modification of the latter method, and Souter and Kark<sup>257</sup> suggested that the Quick prothrombin test can be simplified by the use of stable thromboplastin.

*Clinical Use of Vitamin K.*—Among Adults: There has appeared during the past year a large number of articles which support the evidence presented in last year's review that vitamin K in its natural form or in one of its many synthetic forms is capable of controlling deficiency of prothrombin which occurs in man as the result of deficiency of vitamin K. The entire problem has been fully discussed in recent monographs by Snell and one of us (H. R. B.),<sup>258</sup> Brinkhous<sup>259</sup> and Bay.<sup>260</sup> Several brief discussions of the general problem also have appeared.<sup>261</sup>

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253. Ferguson, J. H.: Stability of Prothrombin in the Presence of Thrombin, *Proc. Soc. Exper. Biol. & Med.* **46**:80-83 (Jan.) 1941. Orr, W. F., Jr., and Moore, D. H.: Studies on Identity of Prothrombin, *ibid.* **46**:357-360 (Feb.) 1941. Shafiroff, B. G. P.; Doubilet, H., and Tui, C. O.: Effect of Intramuscular Injection of Sodium Citrate on the Prothrombin Time of the Blood, *ibid.* **46**:136-139 (Jan.) 1941.

254. Lord, J. W., Jr.; Andrus, W. D., and Moore, R. A.: Metabolism of Vitamin K, and Role of the Liver in Production of Prothrombin in Animals, *Arch. Surg.* **41**:585-595 (Sept.) 1940.

255. Cullen, S. Z.; Ziffren, S. Z.; Gibson, R. V., and Smith, H. T.: Anesthesia and Liver Injury with Special References to Plasma Prothrombin Levels, *J. A. M. A.* **115**:991-994 (Sept. 21) 1940.

256. Herbert, F. K.: The Estimation of Prothrombin in Human Plasma, *Biochem. J.* **34**:1554-1568 (Dec.) 1940.

257. Souter, A. W., and Kark, R.: Quick's Prothrombin Test Simplified by the Use of a Stable Thromboplastin, *Am. J. M. Sc.* **200**:603-607 (Nov.) 1940.

258. Butt, H. R., and Snell, A. M.: Vitamin K, Philadelphia, W. B. Saunders Company, 1941.

259. Brinkhous, K. M.: Plasma Prothrombin, Vitamin K, *Medicine* **19**:329-416 (Sept.) 1940.

260. Bay, R.: Hígado-prothrombina-vitamin K (estudio experimental y clínico), *Bol. Inst. de clín. quir.* **17**:139-231 (Feb.-March) 1941.

261. Kark, R., and Souter, A. W.: Hypoprothrombinaemia and Avitaminosis-K in Man, *Brit. M. J.* **2**:190-194 (Aug. 9) 1941. Smith, H. P., and Owen, C. A.:

Menadione continues to be much favored in the treatment of deficiency of prothrombin. Both the oral and the intravenous form of administration of this compound in most cases have proved to be effective in controlling hypoprothrombinemia.<sup>262</sup> Stewart<sup>262a</sup> observed that the effectiveness of menadione taken by mouth is increased by the taking of desoxycholic acid or bile salts, even in the absence of jaundice. Moreover, this author did not observe any evidence of toxicity, even when as much as 20 mg. of menadione was given intravenously in one dose. Others<sup>262c</sup> confirmed the fact, already established, that the intravenous administration of menadione results in a rapid decrease in an elevated prothrombin clotting time.

Again, the water-soluble compound 4-amino-2-methyl-1-naphthol hydrochloride has proved to be just as effective when administered intravenously as the derivative of menadione.<sup>263</sup> A definite response to the intravenous administration of this compound was noted within three quarters of an hour to one and a half hours after administration.<sup>263d</sup> No toxic effects were observed after doses ranging to as high as 6 mg.

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Vitamin K.: Its Use in Patients with Obstructive Jaundice or with Biliary Fistulas, *Rev. Gastroenterol.* **7**:520-528 (Nov.-Dec.) 1940. Hicks, J. D.: A Review of the Literature Concerning Haemorrhage in Obstructive Jaundice: The Significance of Prothrombin and of Vitamin K Therapy, *M. J. Australia* **1**:46-51 (Jan. 11) 1941. Reid, J.: Prothrombin Deficiency in Disease of the Liver and Bile Passages and Its Treatment with Synthetic Vitamin K, *Brit. M. J.* **1**:4189-4194 (April 19) 1941. Cheney, G.: The Clinical Value of Vitamin K, *J. A. M. A.* **115**:1082-1087 (Sept. 28) 1940. Freeman, S., and Grodins, F. S.: Recent Studies of the Factors Involved in the Coagulation of Blood, Including a Review of Vitamin K, *Internat. Abstr. Surg.* **72**:417-427, 1941; in *Surg., Gynec. & Obst.*, May 1941.

262. (a) Stewart, J. D.: Oral and Parenteral Use of Synthetic Vitamin K-Active Substances in Hypoprothrombinemia, *Surgery* **9**:212-219 (Feb.) 1941. (b) Norcross, J. W., and McFarland, M. D.: Intravenous Use of 2-Methyl-1,4-Naphthoquinone in Hypoprothrombinemia: Clinical Observations, *J. A. M. A.* **115**:2156-2161 (Dec. 21) 1940. (c) Tocantins, L. M., and Jones, H. W.: Hypoprothrombinemia: Effect of Peroral and Parenteral Administration of a Synthetic Vitamin K Substitute (2-Methyl-1,4-Naphthoquinone), *Ann. Surg.* **113**:276-283 (Feb.) 1941. (d) Anderson, E. R.; Karabin, J. E.; Udesky, H. L., and Seed, L.: The Oral Administration of Synthetic Vitamin K (2-Methyl-1,4-Naphthoquinone), *Surgery* **9**:361-371 (March) 1941.

263. (a) Sharp, E. A.; Konder Heide, E. C., and Good, W. H.: Vitamin K Activity of 2-Methyl-1,4-Naphthoquinone and 4-Amino-2-Methyl-1-Naphthol in Hypoprothrombinemia, *J. Lab. & Clin. Med.* **26**:818-822 (Feb.) 1941. (b) Olwin, J. H.: The Intravenous Use of Vitamin K, *J. A. M. A.* **117**:432-435 (Aug. 9) 1941. (c) Emmett, A. D.; Kamm, O., and Sharp, E. A.: The Vitamin K Activity of 4-Amino-2-Methyl-1-Naphthol and 4-Amino-3-Methyl-1-Naphthol, *J. Biol. Chem.* **133**:285-286 (March) 1940. (d) Anderson, E. R.; Karabin, J. E.; Udesky, H., and Seed, L.: Parenteral Administration of a Water-Soluble Compound with Vitamin K Activity: 4-Amino-2-Methyl-1-Naphthol Hydrochloride, *Arch. Surg.* **41**:1244-1250 (Nov.) 1940.

had been administered. It was also suggested by Olwin that 4-amino-2-methyl-1-naphthol hydrochloride, 2-methyl-1,4-naphthohydroquinone-3-sodium sulfonate, 2-methyl-1,4-dihydroxynaphthalene diphosphoric acid ester tetra sodium salt all may be of definite practical use.<sup>263b</sup>

In almost all the clinical studies just mentioned, the synthetic quinone derivatives with vitamin K activity were employed in the treatment of hypoprothrombinemia resulting from obstructive jaundice from one cause or another. In such a condition its clinical use is established without doubt. Some investigators<sup>264</sup> have recently expressed the opinion that the change effected in a particular level of prothrombin by the administration of vitamin K may provide some index as to the nature of the disease being treated, with particular reference to intrahepatic and extra-hepatic jaundice. Data<sup>265</sup> now at hand do not unequivocally establish this fact. Almost all investigators,<sup>266</sup> however, agree that deficiency of prothrombin resulting from severe primary hepatic injury is not controlled by the administration of vitamin K in any amount. Some investigators have contended that there is a correlation between the Quick hippuric acid test for hepatic function and the level of prothrombin in the circulating blood. Recent work<sup>267</sup> does not substantiate this view.

The suggestion that deficiency of prothrombin can occur in various intestinal disturbances continues to be supported.<sup>268</sup> Apparently, such a deficiency is not uncommon in sprue and various forms of idiopathic steatorrhea. Others,<sup>269</sup> in a study of values for prothrombin among patients suffering from pellagra and associated nutritional deficiency states, have observed that deficiency of vitamin K was not common in

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264. Allen, J. G., and Julian, O. C.: Response of Plasma Prothrombin to Vitamin K Substitute Therapy in Cases of Hepatic Disease, *Arch. Surg.* **41**:1363-1365 (Dec.) 1940. Andrus, W. DeW.: The Newer Knowledge of Vitamin K, *Bull. New York Acad. Med.* **17**:116-134 (Feb.) 1941.

265. Butt, H. R.: Unpublished data.

266. (a) Lucia, S. P., and Aggeler, P. M.: The Influence of Liver Damage on the Plasma Prothrombin Concentration and the Response to Vitamin K, *Am. J. M. Sc.* **201**:326-340 (March) 1941. (b) Kark, R.; White, F. W.; Souter, A. W., and Deutsch, E.: Blood Prothrombin Levels and Hippuric Acid Excretion Liver Function Test in Liver Disease, *Proc. Soc. Exper. Biol. & Med.* **46**:424-426 (March) 1941. (c) Butt and Snell.<sup>265</sup> (d) Brinkhaus.<sup>259</sup> (e) Butt.<sup>265</sup>

267. Footnote 266 a and b.

268. Kark, R.; Souter, A. W., and Hayward, J. C.: A Haemorrhagic Diathesis in Idiopathic Steatorrhea: Observations on Its Association with Vitamin K Deficiency, *Quart. J. Med.* **9**:247-261 (Oct.) 1940. Allen, J. G.: The Comparative Prothrombin Responses to Vitamin K and Several of Its Substitutes in a Case of Nontropical Sprue, *New England J. Med.* **224**:195-197 (Jan. 30) 1941. Sharp, Konder Heide and Good.<sup>263a</sup>

269. Warner, E. D.; Spies, T. D., and Owen, C. A.: Hypoprothrombinemia and Vitamin K in Nutritional Deficiency States, *South. M. J.* **34**:161-163 (Feb.) 1941.

cases of these types. They did observe, however, that prolonged diarrhea at times results in a serious deficiency of this vitamin. Many chronically debilitated patients have a moderate deficiency of prothrombin which apparently is due to causes other than deficiency of vitamin K, since administration of vitamin K to these patients does not elevate the level of prothrombin. Chute<sup>270</sup> claimed that vitamin K was of value in the control of abnormal bleeding occurring in a patient suffering from a renal stone who underwent a surgical procedure and in whom fever later developed. Others<sup>271</sup> found that vitamin K was of no effect in the control of pulmonary hemorrhage associated with tuberculosis.

Among Infants: During the past year numerous reports have appeared on the effect of compounds possessing vitamin K activity on the prothrombin level of the newborn infant. The suggestion made more than a year ago by Waddell and Guerry that no surgical procedure be performed on any newborn infant without the prophylactic administration of vitamin K has proved to be eminently sensible.

Several groups of investigators<sup>272</sup> have reestablished the fact that the normal increase in the prothrombin clotting time of the newborn infant will be prevented by administration of vitamin K to the mother prior to delivery and to the newborn infant. Again, it has been emphasized<sup>273</sup> that the intramuscular administration of blood to the newborn

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270. Chute, R.: The Value of Vitamin K in the Treatment of Abnormal Bleeding, *New England J. Med.* **224**:360-361 (Feb. 27) 1941.

271. Kaplan, R. H.: Use of Vitamin K in the Hemoptysis of Pulmonary Tuberculosis, *M. Bull. Vet. Admin.* **18**:48 (July) 1941. Harrell, C. L., and Ray, A. C.: Pulmonary Hemorrhage in Tuberculosis and Thyloquinone or Vitamin K, *Virginia M. Monthly* **68**:451-456 (Aug.) 1941.

272. (a) Lawson, R. B.: Treatment of Hypoprothrombinemia (Hemorrhagic Disease) of the Newborn Infant, *J. Pediat.* **18**:224-234 (Feb.) 1941. (b) Bruchsalter, F. S.: Vitamin K and the Prenatal and Postnatal Prevention of Hemorrhagic Disease in Newborn Infants, *ibid.* **18**:317-320 (March) 1941. (c) Willumsen, H. C.; Stadler, H. E., and Owen, C. A.: Comparative Effect of Vitamin K and Whole Blood on Prothrombin Deficiency of Newborn Infant, *Proc. Soc. Exper. Biol. & Med.* **47**:116-121 (May) 1941. (d) Leidenheimer, H., Jr., and Albritton, A. S.: Studies on the Bleeding Tendency and Vitamin K Therapy in Newborn Children, *New Orleans M. & S. J.* **93**:464-470 (March) 1941. (e) Mull, J. W.; Bill, A. H., and Skowronska, H.: Effect on the Newborn of Vitamin K Administered to Mothers in Labor, *J. Lab. & Clin. Med.* **26**:1305-1309 (May) 1941. (f) Bohlender, G. P.; Rosenbaum, W. M., and Sage, E. C.: Antepartum Use of Vitamin K in the Prevention of Prothrombin Deficiency in the Newborn, *J. A. M. A.* **116**:1763-1766 (April 19) 1941. (g) Snelling, C. E., and Nelsen, W.: Vitamin K in Hemorrhagic Disease of the Newborn Infant, *J. Pediat.* **17**:615-620 (Nov.) 1940. (h) Valentine, E. H.; Reinhold, J. G., and Schneider, E.: The Effectiveness of Prenatal Administration of 2-Methyl-1,4-Naphthoquinone in Maintaining Normal Prothrombin Levels in Infants, *Am. J. M. Sc.* **202**:359-364 (Sept.) 1941.

273. Footnote 272 a and b.

infant is of no advantage in the prophylactic treatment of deficiency of prothrombin. It has been demonstrated<sup>274</sup> that not only is menadione effective in the treatment of the newborn infant but that 2-methyl-1,4-dihydroxynaphthalene diphosphoric acid ester tetra sodium salt also is effective. Others<sup>275</sup> have pointed out that there is no relation between the mother's diet and the postpartum level of prothrombin in the newborn infant. Apparently, a completely adequate diet, as it is understood today, for the pregnant woman is not sufficient to protect the child from the potential danger of hemorrhage. Javert and Macri<sup>276</sup> observed that in normal pregnancy the prothrombin level was 70 per cent or less among 15 per cent of 200 patients. This observation is not in keeping with those made in other reports. In an excellent study Sells and his associates<sup>277</sup> reported that the vitamin K requirement of newborn infants is extremely low. Approximately 1 microgram of synthetic vitamin K is a sufficient daily amount. They suggested that colostrum contains enough free vitamin K to meet this minimal requirement. This work has not yet been confirmed. The successful treatment of erythroblastosis in icterus gravis neonatorum with vitamin K has been reported.<sup>278</sup> For a review of the general subject the reader is referred to two papers.<sup>279</sup>

Vitamin K and its analogues have been successfully administered orally, intramuscularly and intravenously. Recently, it has been reported that it may be possible to administer this compound by inunction. It was first reported by DeBeer and his associates<sup>280</sup> that a synthetic compound possessing vitamin K activity dissolved in a warm mixture of hydrous wool fat and liquid petrolatum could be rubbed underneath the wing of a vitamin K-deficient chick, with resulting effect

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274. McCready, R. L.; Callahan, E. T., and Grandin, D. J.: Parenteral Vitamin K Therapy in Ante-Partum Women and Its Effects on the Infants' Prothrombin Levels: A Preliminary Report, *Am. J. Obst. & Gynec.* **42**:398-404 (Sept.) 1941.

275. Astrowe, P. S.; Palmerton, E. S., and Henderson, V.: Clinical Studies with Vitamin K in Newborn Infants, *J. Pediat.* **18**:507-515 (April) 1941.

276. Javert, C. T., and Macri, C.: Prothrombin Concentration in Normal Pregnancy, *Am. J. Obst. & Gynec.* **42**:415-419 (Sept.) 1941.

277. Sells, R. L.; Walker, S. A., and Owen, C. A.: Vitamin K Requirement of the Newborn Infant, *Proc. Soc. Exper. Biol. & Med.* **47**:441-445 (June) 1941.

278. Mayman, E. W.: Erythroblastosis in Icterus Gravis Neonatorum Successfully Treated with Vitamin K, *J. Pediat.* **17**:806-808 (Dec.) 1940.

279. Grossman, A. M.: Practical Therapy with Vitamin K: A Simple Reclassification of Hemorrhagic Diseases Due to a Deficiency of Blood Prothrombin, *M. Ann. District of Columbia* **10**:218-225 (June) 1941. Savage, H.: The Development of Vitamin K and Its Clinical Uses in the Neonatal Period, *Arch. Dis. Childhood* **16**:67-70 (March) 1941.

280. DeBeer, E. J.; Drektar, L., and Flusser, B.: Routes of Administration of Materials Capable of Acting as Vitamin K, *Proc. Soc. Exper. Biol. & Med.* **46**:535-537 (April) 1941.

on the diminished level of prothrombin. Recently, this experimental knowledge has been applied clinically by Russell and Page.<sup>281</sup> These authors embodied 1 per cent menadione in a specially prepared base. Newborn infants were given 10 mg. of this mixture, applied to the skin of the back, on the first and second days of life. The prothrombin clotting time showed a steady decrease and was within normal limits by the fifth day. No newborn infants treated in this manner exhibited the so-called physiologic deficiency of prothrombin. These authors also described a new method for micromeasurement of prothrombin in which Russell's viper venom was employed. Other authors<sup>278</sup> also have reported microtests for prothrombin.

Two rather extensive studies<sup>282</sup> on this general problem warrant some discussion. Beck and co-workers<sup>282a</sup> reported that only 5, or 0.5 per cent, of 1,022 infants whose mothers had received vitamin K prior to delivery showed any evidence of hemorrhage, in contrast to 21, or 2 per cent, of 1,037 infants (controls) whose mothers had not received vitamin K prior to delivery. In this series of 2,059 cases, in which alternate mothers received vitamin K, it appears that the administration of vitamin K prior to delivery reduced the incidence of hemorrhage in the newborn infant by approximately 75 per cent. These authors gave 2 mg. of menadione by mouth to the mother one-half hour to forty-four hours before delivery. Hellman, Shettles and Eastman<sup>282b</sup> have continued their extensive study of the problem and recently reviewed one year's experience, which should be read by every one interested in prenatal care. These authors have already demonstrated that the plasma level of prothrombin in the newborn infant can be increased by administering vitamin K to the mother, even if it is given as late as four hours before delivery. They found that although the feeding of vitamin K to a baby after birth increased the concentration of prothrombin, the levels of prothrombin in these instances were not so high as those achieved by antepartum administration of the vitamin to the mother. The evidence which they had at hand suggested that many instances of cerebral hemorrhage occurring during birth, with minimal birth trauma, are precipitated by small hemorrhages which endure for a number of days. For this reason, these authors expressed the belief that the lives of some of the infants might have been saved had their blood at birth exhibited better prop-

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281. Russell, H. K., and Page, R. C.: Effect of Topical Application of 2-Methyl-1,4-Naphthoquinone (Synthetic Vitamin K Analogue) on the Prothrombin Level of Newborn Infants, with Reference to a Simplified Microprothrombin Test, *Am. J. M. Sc.* **202**:355-359 (Sept.) 1941.

282. (a) Beck, A. C.; Taylor, E. S., and Colburn, R. F.: Vitamin K Administered to the Mother During Labor as a Prophylaxis Against Hemorrhage in the Newborn Infant, *Am. J. Obst. & Gynec.* **41**:765-775 (May) 1941. (b) Hellman, L. M.; Shettles, L. B., and Eastman, N. J.: Vitamin K in Obstetrics: A Review of One Year's Experience, *ibid.* **40**:844-853 (Nov.) 1940.

erties of coagulation. Beginning on Sept. 1, 1939, every other patient in labor admitted to the obstetric service at the Johns Hopkins Hospital received vitamin K by mouth. Menadione in a single dose of 2 mg. was employed. By May 1, 1940, 384 mothers had received vitamin K in labor, whereas in the control series there were 392 patients. No specific effect was noted on postpartum hemorrhage after administration of vitamin K, and the weight of infants at discharge from the hospital in relation to the weight at birth was about the same in the two groups. The rate for stillbirths and neonatal mortality was 16 deaths, or 4.1 per cent, in the control series; in the series in which vitamin K had been used there were 6 deaths, or a mortality rate of 1.5 per cent. The infant death rate in the control series accordingly was two and seven-tenths times that of the series in which vitamin K had been administered. In studies of these infants at necropsy an interesting fact was noted: In only 1 of the 6 dead infants whose mothers had received vitamin K was hemorrhage demonstrable. This infant had been born by breech delivery, and necropsy disclosed subarachnoidal hemorrhage. In the control series, hemorrhage into one or another organ was demonstrable at necropsy in 9, or 56 per cent, of the 16 infants. In 3 cases extensive cerebral hemorrhage was present to account for the death of the infant. In a study of the retinas of 92 infants in the control group, hemorrhage was demonstrable in 29, or 32 per cent. Among the 75 infants whose mothers had received vitamin K, retinal hemorrhages were demonstrable in 12, or 16 per cent. Therefore, the frequency of retinal hemorrhage in the control group was twice that in the group of infants whose mothers had been treated prophylactically with vitamin K.

#### OTHER VITAMINS

During the past year many references have appeared in association with studies on vitamin H, or biotin.<sup>283</sup> Soon it was confirmed that

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283. György, P.: The Curative Factor (Vitamin H) for Egg White Injury, with Particular Reference to Its Presence in Different Foodstuffs and in Yeast, *J. Biol. Chem.* **131**:733-744 (Dec.) 1939. Birch, T. W., and György, P.: Physicochemical Properties of the Factor (Vitamin H) Curative of Egg White Injury, *ibid.* **131**:761-766 (Dec.) 1939. György, P.; Kuhn, R., and Lederer, E.: Attempts to Isolate the Factor (Vitamin H) Curative of Egg White Injury, *ibid.* **131**:745-759 (Dec.) 1939. Eakin, R. E.; Snell, E. E., and Williams, R. J.: A Constituent of Raw Egg White Capable of Inactivating Biotin in Vitro, *ibid.* **136**:801-802 (Dec.) 1940. Hottle, G. A.; Lampen, J. O., and Pappenheimer, A. M., Jr.: Biotin as a Growth Factor for C203S Strain of Hemolytic *Streptococcus* Group A, *ibid.* **137**:457-458 (Jan.) 1941. McElroy, L. W., and Jukes, T. H.: Formation of the Anti Egg-White-Injury Factor (Biotin) in the Rumen of the Cow, *Proc. Soc. Exper. Biol. & Med.* **45**:296-297 (Oct.) 1940. György, P.; Melville, D. B.; Burk, D., and du Vigneaud, V.: The Possible Identity of Vitamin H with Biotin and Coenzyme R, *Science* **91**:243-245 (March 8) 1940.



vitamin H and biotin were identical,<sup>284</sup> and recently a method was described<sup>285</sup> for the isolation of a methyl ester of biotin from the liver. The analytic data agreed most closely with the empiric formula  $C_{11}H_{18}O_3N_2S$ .

Ansbacher,<sup>286</sup> during the past year, reported that paraaminobenzoic acid was a vitamin and that it possessed a chromotrichia factor for the rat and a growth-promoting factor for the chick. On the basis of his studies on rats and chicks, he concluded that this compound was one of the factors of the vitamin B complex. This acid also apparently modifies the formation of melanin<sup>287</sup> and when administered to man will result in the turning of gray hair to black.<sup>288</sup>

Vitamin L continues to be mentioned. It has been reported that subsistence on a dextrin diet leads to the production of vitamin L<sub>2</sub> by the intestinal yeasts.<sup>289</sup>

Recent experimental work has given rise to evidence that vitamin P may be of value in the control of vascular purpura. Rusznyák and Benkó<sup>290</sup> have shown that the administration of this factor will correct diminished capillary resistance both in guinea pigs and in rats. This is in agreement with the previous observations of Scarborough<sup>291</sup> concerning human beings. He wrote that two forms of subcutaneous hemorrhage may appear in deficiency states, due individually to deficiency of vitamins C and P. He expressed the belief that only vitamin P deficiency states are associated with a low capillary resistance. Rapaport and Klein<sup>292</sup> were able to duplicate this reduction of the

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284. du Vigneaud, V.; Melville, D. A.; György, P., and Rose, C. F.: On the Identity of Vitamin H with Biotin, *Science* **92**:62-63 (July 19) 1940. Porter, J. R., and Pelczar, M. J., Jr.: The Nutrition of *Staphylococcus Aureus*: The Influence of Biotin, Bios II<sub>B</sub> and Vitamin H on the Growth of Several Strains, *J. Bact.* **41**:173-192 (Feb.) 1941. György, P.; Rose, C. S.; Hofmann, K.; Melville, D. B., and du Vigneaud, V.: A Further Note on the Identity of Vitamin H with Biotin, *Science* **92**:609 (Dec. 27) 1940.

285. du Vigneaud, V.; Hofmann, K.; Melville, D. B., and György, P.: Isolation of Biotin (Vitamin H) from Liver, *J. Biol. Chem.* **140**:643-651 (Aug.) 1941.

286. Ansbacher, S.: *p*-Aminobenzoic Acid, a Vitamin, *Science* **93**:164-165 (Feb. 14) 1941.

287. Martin, G. J.; Wisansky, W. A., and Ansbacher, S.: Para-Aminobenzoic Acid and Dopa Reaction, *Proc. Soc. Exper. Biol. & Med.* **47**:26-28 (May) 1941.

288. Sieve, B. F.: Clinical Achromotrichia, *Science* **94**:257-258 (Sept. 12) 1941.

289. Nakahara, W.; Inukai, F., and Ugami, S.: Vitamin L and Dextrin Diet, *Science* **93**:39-40 (Jan. 10) 1941.

290. Rusznyák, S., and Benkó, A.: Experimental Vitamin P Deficiency, *Science* **94**:25 (July 4) 1941.

291. Scarborough, H.: Deficiency of Vitamin C and Vitamin P in Man, *Lancet* **2**:644-647 (Nov. 23) 1940.

292. Rapaport, H. G., and Klein, S.: Vitamin P and Capillary Fragility, *J. Pediat.* **18**:321-327 (March) 1941.

capillary fragility in 100 allergic children. Other investigators have found vitamin P to be effective against allergic purpura,<sup>293</sup> infectious purpura,<sup>293</sup> purpura of measles,<sup>294</sup> purpura which occurs after arsenic therapy<sup>295</sup> and psoriasis.<sup>296</sup>

#### THE WASHINGTON YARDSTICK FOR NUTRITION

Of great significance for policy direction in current governmental activities designed to raise the nutritive quality of American diets was action taken by the Committee on Food and Nutrition and announced in May 1941 at the National Nutrition Conference for Defense. This committee was organized at the request of the government to advise on the scientific aspects of problems of nutrition in connection with national defense. Its early deliberations gave rise to the formulation of recommended daily allowances for those specific nutrients—protein, calcium, iron, vitamin A, thiamine, riboflavin, nicotinic acid and ascorbic acid—for which a human need has been clearly established. The recommended allowances are contained in the table. The recommendations were based on a critical appraisal of the literature and on opinions obtained from a considerable number of authorities on nutrition in various parts of the United States. They are believed to represent the combined judgment of American authorities on the amounts of the various nutritive essentials which it is desirable to include in practical diets. The term “recommended allowances” rather than “standards” or “optimal allowances” was used to avoid the implication of finality, and the urgent need for continued research on human needs was emphasized.

#### FORTIFICATION OF FOODS WITH VITAMINS AND MINERALS

Enriched flour, that is, plain white flour with thiamine, nicotinic acid and iron added in amounts such that the content of these nutrients approximates the content of them in whole wheat flour, appeared early in January 1941.<sup>297</sup> Enriched bread soon followed. This procedure was based on recommendations of the Committee on Food and Nutrition

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293. Kugelmass, I. N.: Vitamin P in Vascular Purpura, *J. A. M. A.* **115**:519-520 (Aug. 17) 1940.

294. Miller, A. A.: Purpura in the Course of Measles: A Case Treated with Vitamin P, *Brit. J. Child. Dis.* **38**:1-14 (Jan.-March) 1941.

295. Gorrie, D. R.: Purpura Haemorrhagica After Arsenic Therapy Treated with Vitamin P, *Lancet* **1**:1005-1007 (June 1) 1940.

296. Goldfarb, A. E.: Treatment of Psoriasis with Lemon Citrin (Vitamin P), Citrin Lemonade and Ascorbic Acid, *Arch. Dermat. & Syph.* **43**:536-538 (March) 1941.

297. Vitamin-Enriched Flour Goes into Production, *Science News Letter* **39**: 83-84 (Feb. 8) 1941.

of the National Research Council.<sup>298</sup> It received the endorsements of the National Nutrition Conference for Defense, the Council on Foods and Nutrition and the House of Delegates of the American Medical Association. The general principle involved followed closely a policy adopted early in 1939 by the Council on Foods and Nutrition of the American Medical Association.<sup>298c</sup> The manufacture and distribution

*Recommended Daily Allowances for Specific Nutrients Recommended by the Committee on Foods and Nutrition, National Research Council\**

	Calo- ries	Pro- tein, Gm.	Cal- cium, Gm.	Iron, Mg.	Vita- min A, Inter- national Units†	Thia- mine (Vita- min B <sub>1</sub> ), Mg.‡	Ribo- flavin, Mg.	Nico- tic Acid, Mg.	As- corbic Acid, Mg.§	Vita- min D, Inter- national Units
<b>Man (70 Kg.)</b>										
Moderately active....	3,000	70	0.8	12	5,000	1.8	2.7	18	75	
Active.....	4,500	..	..	..	.....	2.3	3.3	23		
Sedentary.....	2,500	..	..	..	.....	1.5	2.2	15		
<b>Woman (56 Kg.)</b>										
Moderately active....	2,500	60	0.8	12	5,000	1.5	2.2	15	70	
Active.....	3,000	..	..	..	.....	1.8	2.7	18		
Sedentary.....	2,100	..	..	..	.....	1.2	1.8	12		
Pregnant (in latter half of pregnancy)..	2,500	85	1.5	15	6,000	1.8	2.5	18	100	400-800
Lactating.....	3,000	100	2.0	15	8,000	2.3	3.0	23	150	400-800
<b>Children up to 12 years</b>										
Under 1 year ¶.....	100/Kg. 3-4 Kg.	1.0	6	1,500	0.4	0.6	4	30	400-800	
1 to 3 years #.....	1,200	40	1.0	7	2,000	0.6	0.9	6	35	
4 to 6 years.....	1,600	50	1.0	8	2,500	0.8	1.2	8	50	
7 to 9 years.....	2,000	60	1.0	10	3,500	1.0	1.5	10	60	
10 to 12 years.....	2,500	70	1.0	12	4,500	1.2	1.8	12	75	
<b>Children over 12 years</b>										
Girls, 13 to 15 years..	2,800	80	1.3	15	5,000	1.4	2.0	14	80	
16 to 20 years..	2,400	75	1.0	15	5,000	1.2	1.8	12	80	
Boys, 13 to 15 years..	3,200	85	1.4	15	5,000	1.6	2.4	16	90	
16 to 20 years..	3,800	100	1.4	15	6,000	2.0	3.0	20	100	

\* Adapted from "Recommended Dietary Allowances," Nutrition Division, Federal Security Agency, Washington, D. C. These recommendations represent a tentative goal toward which to aim in planning practical dietaries and can be met by a good diet of natural foods. Such a diet will also provide other minerals and vitamins, the requirements for which are less well known.

† The requirements may be less of vitamin A as such is provided or greater if it is provided chiefly as the provitamin carotene.

‡ One milligram of thiamine hydrochloride equals 333 international units.

§ One milligram of ascorbic acid equals 20 international units.

¶ Vitamin D is undoubtedly necessary for older children and adults. When it is not available from sunshine it should be provided probably up to the minimum amount recommended for infants.

‡ The needs of infants increase from month to month. The amounts given are for infants about 6 to 8 months old. The amounts of protein and calcium may be less if they are derived from breast milk.

# The allowances are based on the needs for the middle year in each group (2, 5, 8, etc.) and for moderate activity.

of enriched flour and bread have been proceeding rapidly. By the end of July 1941, 3,500,000,000 of the 10,500,000,000 pounds (1,600,-

298. (a) Wilder, R. M.: Nutrition Planning for the National Defense, War Med. **1**:143-157 (March) 1941; (b) Nutrition in the United States: A Program for the Present Emergency and the Future, Ann. Int. Med. **14**:2189-2198 (June) 1941; (c) Vitamin Restoration of Foods as Viewed by the Physician, Scient. Monthly **53**:295-302 (Oct.) 1941. (d) Williams, R. R.: Fortification and Restoration of Processed Foods, Indust. & Engin. Chem. (Indust. Ed.) **33**:718-720 (June 2) 1941.

000,000 of the 4,760,000,000 Kg.) of bakers' bread consumed annually in the United States was enriched bread<sup>299</sup> and more than 40 per cent of the flour for family use on the market was enriched.<sup>300</sup>

New evidence supporting the belief that enriched flour and bread represent products of superior nutritional value was presented by Elvehjem at the public hearings on bread held by the Food and Drug Administration during July and August 1941.<sup>301</sup> His analyses showed that whereas unenriched white flour contains little more than 10 per cent of the thiamine and nicotinic acid of the wheat from which it is made, it contains as much as 50 per cent of the riboflavin, the pyridoxine, the pantothenic acid and the biotin. Also introduced into the same hearings were data obtained by Williams and Higgins<sup>301</sup> which showed that young rats subsisting on human diets grew nearly as well when the flour quota of the diet—representing 25 per cent of the calories—was enriched flour as when this quota consisted of whole wheat flour.

The Committee on Food and Nutrition of the National Research Council also recommended iodization of table salt to a value of 1 part of potassium iodide or equivalent per 10,000 parts of salt and fortification of oleomargarine with vitamin A to a value of 9,000 international units to the pound (18,000 international units per kilogram). The committee encouraged the use of whole wheat bread and of butter but recommended that when these foods are not used, enriched flour and bread and properly fortified oleomargarine are preferred over unenriched white flour and bread and unfortified oleomargarine.

The Committee on Food and Nutrition made public on Oct. 1, 1941, the following recommendation as to policy in the matter of the addition of specific nutrients to foods:

*Resolution Relating to Addition of Specific Nutrients to Foods Adopted by the Committee on Food and Nutrition at Its Meeting in Washington, October 1, 1941.*<sup>302</sup>

WHEREAS there exist deficiencies of vitamins and minerals in the diets of significant segments of the population of the United States which cannot promptly be corrected by public education in the proper choice of foods, be it resolved, in order to correct and prevent such deficiencies:

(1) That the Committee endorses the addition of specific nutrients to staple foods (as indicated under 6 below) which are effective vehicles for correcting the above deficiencies in the diets of the general population or of significant age, geographical, economic or racial segments thereof;

299. Tobey, J. A., and Cathcart, W. H.: *What's New in Home Economics*, (Sept.) 1941.

300. Proceedings American Bakers' Association Conference, Boston, October 14, 1941.

301. Food and Drug Administration Hearings in the Matter of a Definition and Standard of Identity for Bread, July 7—August 15, 1941.

302. Minutes of the Committee on Food and Nutrition, National Research Council, Oct. 1, 1941. The Committee on Food and Nutrition has recently been reorganized and is now known as the Food and Nutrition Board of the National Research Council.

(2) That the Committee opposes the inclusion of additions of specific nutrients under definitions and standards which may be promulgated under the Food, Drug and Cosmetic Act except in the case of foods which constitute such effective vehicles of distribution;

(3) That the Committee favors unequivocally the fulfillment of the nutritional needs of the people by the use of natural foods as far as practicable and to that end encourages education in the proper choice of foods and the betterment of processes of food manufacture and preparation so as to retain more fully the essential nutrients native thereto;

(4) That to avoid undue artificiality of food supply the Committee favors whenever practicable the choice as vehicles for the corrective distribution of vitamins and minerals those foods which have suffered losses in refining processes and recommends that the vitamins and minerals added to such foods should preferably be the kinds and quantities native thereto in the unrefined state;

(5) That the addition of other than natural levels of vitamins and minerals to foods which are suitable as vehicles of distribution may be sanctioned when more natural routes are practically unavailable as measures to correct known nutritional deficiencies;

(6) That at present the Committee favors appropriate enrichment of flour and bread, (and perhaps corn meal), the fortification of milk with vitamin D, the suitable addition of vitamin A to table fats and of iodine to salt for dietary use. There is no information available to the Committee at the present time which indicates that it is desirable to recommend the addition of vitamins or minerals to foods other than those named;

(7) That specifically the Committee opposes the addition of synthetic vitamins to carbonated beverages and confectionery.

#### THE NATIONAL NUTRITION CONFERENCE FOR DEFENSE

This conference, called by the President of the United States, met in Washington, D. C., May 26 to 28, 1941.<sup>303</sup> It was attended by 700 invited delegates who represented the principal organizations, lay and public, with interests in nutrition. Scientists, educators, farmers, distributors, consumers and public officials in sectional and general meetings gave broad consideration to the questions raised by the problem of human needs for foods. They considered the question of the provision of satisfactory foods, first, as a measure of defense through improvement of the vigor and morale of the people of the United States; second, as a weapon of defense for all the democracies, and in particular Great Britain, and, third, as a basis for far reaching benefits to public health which in future years may accrue. As reported by Parran,<sup>304</sup> detailed agreement on methods, on lines of attack or on emphasis was not always obtained.

303. Proceedings of the National Nutrition Conference for Defense, Washington, D. C., Government Printing Office, to be published.

304. Parran, T.: Nutrition for National Defense, *New Republic* **104**:786-788 (June 9) 1941.

But the final recommendations, arrived at by the democratic processes of group give-and-take, represented basic practical next steps. Presented at the closing session of the conference by Dr. M. L. Wilson, director of the Division of Nutrition, Office of Defense Health and Welfare Services, they were unanimously adopted. In brief they called for the following actions:

1. The use of the standards prepared by the Committee on Food and Nutrition, both as the general goal for good nutrition in the United States and as the yardstick by which to measure progress.

2. Translation of these allowances, and other technical material, into terms of everyday foods and appetizing meals suitable for families and individuals at different economic levels.

3. Vigorous and continuous research to add to present knowledge of all aspects of nutrition.

4. More widespread education in nutrition of physicians, dentists, social service workers, teachers, etc.

5. The mobilization of every educational method to reach laymen by means of the schools, motion pictures, the radio, the public press, home and community demonstrations and all other suitable means.

6. Mobilization of all neighborhood, community, state and national organizations and services that can contribute in any way to raising the nutritional level of the people.

7. Vigorous and continued attack on the fundamental problems of unemployment, insecure employment and rates of pay inadequate to maintain an American standard of living.

8. Full use of any practical devices, such as the Food Stamp Plan, free school lunches and low cost milk distribution, which will bring nourishing, adequate meals to those who could not otherwise afford them and at the same time help to distribute food surpluses at a fair return to the farmer.

9. Efforts to improve food distribution, including processing, marketing, packaging and labeling, to bring about greater real economies for the consumer. These efforts would include vigorous prosecution of illegal practices.

10. Encouragement in all practical ways of greater production of the foods needed in more abundance—milk and milk products, eggs, vegetables, fruits and, in the case of many families, lean meats.

11. Encouragement in every practical way of more production for home use by rural people, especially those at low income levels.

12. The "enrichment" of certain staple food products, such as flour and bread, with nutritive elements that have been removed by modern milling and refining processes.

# DISEASES OF METABOLISM

## REVIEW OF CERTAIN RECENT CONTRIBUTIONS

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As in our review of last year, we shall summarize certain of the more significant contributions of the past year in the field of metabolic disturbances, with particular emphasis on the two most important disturbances of carbohydrate metabolism, diabetes mellitus and spontaneous hypoglycemia, as well as obesity, adrenal cortical insufficiency and disorders of the pituitary body and of the thyroid gland. Some discrimination had to be made in the selection of the articles referred to, since not all, as is usually true, were of equal merit. An effort has been made to give reference to both sides of controversial questions, without the formation of any conclusions on our part.

### DIABETES MELLITUS

*Carbohydrate Metabolism.*—Fantl and his associates<sup>1</sup> recently have reported results of a detailed study of glycogen metabolism in the intact liver of the rabbit. Their work confirmed the essential points in Cori's<sup>2</sup> previous extensive observations on this same subject, namely, that the breakdown of glycogen to dextrose involves a series of well defined intermediate reactions in which phosphorylation of the intermediary products plays a major part.

Soskin<sup>3</sup> has continued his work on the importance of the hepatic regulation of the concentration of the sugar of the blood in connection with the disturbance of carbohydrate metabolism in diabetes mellitus. He reemphasized the fact that the diabetic animal can and does metabolize both carbohydrates and ketone bodies. In the absence of insulin, the

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1. Fantl, P.; Anderson, C. M., and Nelson, J. F.: Concerning Glycogen Breakdown in the Liver, *Australian J. Exper. Biol. & M. Sc.* **18**:369-377 (Dec.) 1940.

2. Cori, C. F.: Symposium on Carbohydrate Metabolism: Glycogen Breakdown and Synthesis in Animal Tissues, *Endocrinology* **26**:285-296 (Feb.) 1940.

3. Soskin, S.: The Blood Sugar: Its Origin, Regulation and Utilization. *Physiol. Rev.* **21**:140-193 (Jan.) 1941.

diabetic animal can utilize carbohydrates at any rate of which the normal animal is capable but utilizes less dextrose than the latter animal when the comparison is made at the same blood sugar level. Even this difference disappears above certain high blood sugar levels, whether or not insulin is present. Insulin merely modifies the relation between the concentration of the sugar in the blood and the rate of reaction, accelerating some phase of carbohydrate metabolism which proceeds slowly in its absence. Soskin pointed out that the threshold of stimulation of the hepatic mechanism, the so-called homeostatic mechanism on which regulation of the glycemic level depends, is in turn dependent on the balance between the blood sugar-lowering hormone, insulin, and the blood sugar-elevating hormones of the anterior lobe of the pituitary body and probably also those of the thyroid gland and of the adrenal cortex. Under certain circumstances, therefore, injected insulin may serve not to compensate for deficient secretion of the aforementioned hormone by the pancreas but to restore the endocrine balance to normal.

*Endocrine Relation in Diabetes Mellitus.*—Study of the relation of the anterior lobe of the pituitary body to the cause of diabetes mellitus has been continued by several investigators. Dohan and associates<sup>4</sup> have confirmed Richardson's<sup>5</sup> conclusion that the induction of permanent diabetes mellitus in experimental animals by the repeated injection of extract of the anterior lobe of the pituitary body is associated with atrophy of the islets of Langerhans, particularly of the beta cells. It is this atrophy which probably is responsible for the permanence of the diabetic state. Insulin therapy during the early months of this type of diabetes inhibited the rate of progress of the disease; fasting and fat feeding were followed by temporary diminution of the severity of the disease.

Gaebler and Galbraith<sup>6</sup> reported that in insulin-treated, depancreatized animals receiving constant diets a single large injection of a preparation of the anterior lobe of the pituitary body would produce hyperglycemia, increased glycosuria, ketonuria and hyperlipemia, along with loss of nitrogen. They stated that the dextrose-nitrogen ratios obtained for these animals permitted the assumption that the increase

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4. Dohan, F. C.; Fish, C. A., and Lukens, F. D. W.: Induction and Course of Permanent Diabetes Produced by Anterior Pituitary Extract, *Endocrinology* **28**:341-357 (March) 1941.

5. Richardson, K. C.: Influence of Diabetogenic Anterior Pituitary Extracts of the Islets of Langerhans in Dogs, *Proc. Roy. Soc., London, s.B* **128**:153-169 (Jan. 4) 1940.

6. Gaebler, O. H., and Galbraith, H. W.: Effects of Anterior Pituitary Preparations in Experimental Pancreatic Diabetes, *Endocrinology* **28**:171-178 (Feb.) 1941.



in glycosuria was due to two factors, namely, increased formation of dextrose from protein and interference with the utilization of the dextrose thus produced.

Sakai<sup>7</sup> found glycosuria in 9 of 14 cases of acromegaly, in 3 of which hyperglycemia and the diabetic type of dextrose tolerance curve also were present. He expressed the belief that in the latter cases the disturbance in carbohydrate metabolism was extrainsular in origin and that it probably was related to the pituitary disturbance. Mayer and associates,<sup>8</sup> however, made perimetric studies on 65 unselected diabetic patients and found no evidence that hypertrophy of the pituitary body occurred in a significant number.

White<sup>9</sup> has reaffirmed her earlier statement that the anterior lobe of the pituitary body is hyperactive at the onset of diabetes in children and that subsequently it is hypoactive, so that in some instances a so-called pituitary type of dwarfism may ensue. She reported additional instances of this condition and expressed the belief that the injection of anterior pituitary extract greatly increased the rate of growth. Greene and co-workers<sup>10</sup> reported that extracts of the anterior lobe of the pituitary body increased the rate of growth and the sexual development of 3 young diabetic dwarfs; however, improved control of the diabetes was instituted along with the pituitary therapy and may have played a significant part in the improvement shown by these patients. Chase,<sup>11</sup> among others, argued that good control of the diabetes alone will enable diabetic children to grow and develop normally.

Several authors (Barnes and co-workers,<sup>12</sup> Spiegelman,<sup>13</sup> Cantilo<sup>14</sup>) have reported that the administration of estrogen either to depancreatized

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7. Sakai, T.: Studies on Function of Hypophysis in Carbohydrate Metabolism, Tokyo Igakkwai Zassi **55**:189-190 (March) 1941.

8. Mayer, L. L.; Strouse, C. D., and Soskin, S.: Lack of Perimetric Evidence for Pituitary Hypertrophy in Diabetes, *J. Clin. Endocrinol.* **1**:604-606 (July) 1941.

9. White, P.: Diabetes in Youth, *New England J. Med.* **224**:586-589 (April 3) 1941.

10. Greene, J. A.; January, L. E., and Swanson, L. W.: Effect of Extracts of Anterior Lobe of the Pituitary Gland on Diabetes, Retarded Growth and Sexual Development, *J. A. M. A.* **116**:2531 (May 31) 1941.

11. Chase, L. A.: Diabetes Mellitus: Problems of Its Control, *Canad. M. A. J.* **44**:250-255 (March) 1941.

12. Barnes, B. O.; Regan, J. F., and Nelson, W. O.: Improvement in Experimental Diabetes Following the Administration of Amniotin, *J. A. M. A.* **101**:926-927 (Sept. 16) 1933.

13. Spiegelman, A. R.: Influence of Estrogen on the Insulin Requirement of the Diabetic, *Proc. Soc. Exper. Biol. & Med.* **43**:307-308 (Feb.) 1940.

14. Cantilo, E.: Successful Responses in Diabetes Mellitus of the Menopause Produced by Antagonistic Action of the Sex Hormones in Pituitary Activity, *Endocrinology* **28**:20-24 (Jan.) 1941.

animals or to diabetic patients reduces their requirement of insulin, presumably by suppression of the function of the anterior lobe of the pituitary gland. Lawrence and Madders,<sup>15</sup> however, reported negative results in their treatment of 5 diabetic women who were in the menopausal age group. These patients received 1 mg. of diethylstilbestrol four times daily for eight weeks. No change in their requirement of insulin was noted.

Not only hypophysectomy (Houssay and Biasotti<sup>16</sup>) but bilateral adrenalectomy (Long and associates<sup>17</sup>) has been reported to reduce the severity of diabetes in depancreatized animals. Furthermore, Hampton<sup>18</sup> found that patients who had Addison's disease were hypersensitive to injected insulin. It is therefore interesting to note Rhind and Wilson's<sup>19</sup> report of a fifteenth patient in whom Addison's disease and diabetes mellitus occurred simultaneously. These authors, however, expressed doubt that 5 of the 14 previously described patients could be considered authentically to have the two diseases. In the case which they reported, diabetes was discovered one year after the diagnosis of Addison's disease had been made and treatment with desoxycorticosterone acetate had been begun. As much as 60 units of regular insulin had been required daily for two months; then the patient died from an accidental overdose of insulin. At the postmortem examination atrophy of the adrenal bodies, fibrosis of the islets of Langerhans and a chromophobe adenoma of the pituitary body were found.

*Diagnosis.*—Results of recent examinations of a large number of young men for induction into the army again have called attention to the importance of careful study of those who exhibit glycosuria. Peel and Peel,<sup>20</sup> of Glasgow, Scotland, found that 43 of 115 recruits referred to them because of glycosuria had the diabetic type of dextrose tolerance curve. Beardwood<sup>21</sup> reported an even higher incidence of true diabetes mellitus among patients with glycosuria; he stated that only 8 to 10 per cent of these patients with glycosuria could be considered to have renal

15. Lawrence, R. D., and Madders, K.: Human Diabetes Treated with Oestrogens, *Lancet* **1**:601-602 (May 10) 1941.

16. Houssay, B. A., and Biasotti, A.: The Hypophysis, Carbohydrate Metabolism and Diabetes, *Endocrinology* **15**:511-523 (Nov.-Dec.) 1931.

17. Long, C. N. H.; Katzin, B., and Fry, E. G.: The Adrenal Cortex and Carbohydrate Metabolism, *Endocrinology* **26**:309-344 (Feb.) 1940.

18. Hampton, H. P.: Personal communication to the authors.

19. Rhind, E. G. G., and Wilson, A.: Diabetes Mellitus in Addison's Disease, *Lancet* **2**:37-38 (July 12) 1941.

20. Peel, A. A. F., and Peel, M. W.: Glycosuria in Recruits, *Glasgow M. J.* **17**:141-144 (May) 1941.

21. Beardwood, J. T., Jr.: Modern Diabetic Care, *Pennsylvania M. J.* **44**: 1022-1025 (May) 1941.

glycosuria. Joslin<sup>22</sup> stated that all patients with glycosuria should be reexamined at intervals, since in his experience true diabetes eventually will develop among 6 per cent of them. Yardumian and Alpern<sup>23</sup> reported that there was no fixed renal threshold for dextrose among persons as a group, either in health or in disease. The renal status, the concentration of sugar in the blood and the general condition of the patient (presence of infection, gangrene and the like) might cause rather wide fluctuations in his renal threshold for sugar.

*Mortality Rate.*—Records concerning diabetes collected from large clinics indicate that with the introduction of insulin diabetic coma has largely disappeared as a cause of death. Zisserman<sup>24</sup> found that diabetic coma was the cause of death in only 3.9 per cent of a series of patients whom he studied; coma accounted for only 3.3 per cent of the deaths in Dry and Tessmer's<sup>25</sup> series. On the other hand, insulin appears to have had no favorable effect on the mortality rate arising from cardiovascular complications. Data now available clearly indicate that cardiovascular disease is the chief cause of death of patients who have diabetes. Gangrene of the extremities ranked first and myocardial disease or involvement of the coronary arteries second in the statistics on mortality presented by several authors (Dillon,<sup>26</sup> Zisserman,<sup>24</sup> Pollack and associates,<sup>27</sup> Dry and Tessmer<sup>25</sup>). The principal reasons for these observations would seem to be (1) that the average diabetic patient's life span has been prolonged, so that he now reaches an age at which such vascular complications are common, and (2) that cardiovascular disturbances apparently develop among diabetic patients several years earlier than they do among non-diabetic persons (Beardwood,<sup>21</sup> Dry and Tessmer<sup>25</sup>).

*Treatment.*—Confirmation of the report by Tolstoi and Weber<sup>28</sup> in 1940 concerning the advisability of disregarding both hyperglycemia

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22. Joslin, E. P.: Diabetic Hazards, New England J. Med. **224**:589-592 (April 3) 1941.

23. Yardumian, K. Y., and Alpern, A. N.: Clinical and Laboratory Observations on So-Called "Kidney Threshold for Glucose," Am. J. Clin. Path. **11**: 425-442 (May) 1941.

24. Zisserman, L.: Diabetes Mellitus: A Survey of One Hundred and Fifty-Five Deaths in Diabetic Patients, J. Clin. Endocrinol. **1**:314-315 (April) 1941.

25. Dry, T. J., and Tessmer, C. F.: Postmortem Findings in Cases of Diabetes, Minnesota Med. **24**:96-105 (Feb.) 1941.

26. Dillon, E. S.: Mortality Studies of Diabetes, Pennsylvania M. J. **44**: 1003-1007 (May) 1941.

27. Pollack, H.; Dolger, H., and Ellenberg, M.: An Analysis of the Diabetic Morbidity and Mortality in a General Hospital, Am. J. M. Sc. **202**:246-251 (Aug.) 1941.

28. Tolstoi, E., and Weber, F. C., Jr.: Protamine Zinc Insulin: A Clinical Study; Report of a Group of Diabetic Patients in Whose Cases Glycosuria Was Disregarded for One Year, Arch. Int. Med. **66**:670-678 (Sept.) 1940.

and glycosuria among patients treated with protamine zinc insulin has not appeared in recent literature. Many authors (Beardwood,<sup>21</sup> Marble,<sup>29</sup> Mitchell<sup>30</sup>) still insist on control not only of glycosuria but of hyperglycemia.

The possibility of a "cure" for early diabetes has been discussed this year by McDaniel and his associates.<sup>31</sup> They reported that early and vigorous treatment of diabetes by means of restricted carbohydrate diets and insulin "seemed" in some cases to have brought about an unexpected degree of amelioration of the severity of the disease. In other cases, however, such therapy brought about only the anticipated degree of improvement. The authors recommended the use of procedures designed to "rest" the pancreas, namely, fasting, feeding of fats and the taking of insulin to prevent degenerative changes in islet cells not already affected and to permit restoration of those exhausted cells which still retain the ability to recover.

In this respect the experiments of Richter and Schmidt<sup>32</sup> on depancreatized rats are of interest. These animals when allowed to select their own diet showed a marked appetite for fats and little appetite for carbohydrates. Either a great reduction in or a complete disappearance of both diabetic symptoms and hyperglycemia resulted from the ingestion of these self-selected diets. Normal rats already subsisting on self-selected diets at the time of pancreatectomy likewise exhibited an increased appetite for fats, and diabetic symptoms did not develop until the animals were fed standard rations.

*Insulin.*—Search continues for a type of insulin which can be administered effectively by mouth. Transient hypoglycemic effects have been observed among both animals and human beings to whom mixtures of unmodified insulin and agents designed to promote gastrointestinal absorption (quinine; hexylresorcinol) have been administered orally or rectally. Although huge doses (500 to 1,500 units) of insulin have been administered in this manner, the blood sugar-lowering effects have been so slight and so brief as to make the clinical use of such mixtures

29. Marble, A.: The Treatment of Diabetes with Diet and Insulin, *New England J. Med.* **224**:583-586 (April 3) 1941.

30. Mitchell, J. W.: Treatment of Diabetes in the Aged, *Pennsylvania M. J.* **44**:1015-1018 (May) 1941.

31. McDaniel, L. T.; Marble, A., and Joslin, E. P.: Can Diabetes Be "Cured" by Early, Vigorous Treatment? *Connecticut M. J.* **4**:710-718 (Dec.) 1940.

32. Richter, C. P., and Schmidt, E. C. H., Jr.: Increased Fat and Decreased Carbohydrate Appetite of Pancreatectomized Rats, *Endocrinology* **28**:179-192 (Feb.) 1941.

impracticable (Hanzlik and Cutting,<sup>33</sup> Cutting and Robson,<sup>34</sup> Driver and Murlin<sup>35</sup>).

Additional studies on the subcutaneous implantation of pellets of insulin in combination with cholesterol or lecithin have been carried out by Cutting and associates.<sup>36</sup> In some instances the hypoglycemic effect of such pellets implanted in dogs lasted as long as thirteen days, but the irregularities of absorption were too great to justify clinical trial of the pellets.

There is still argument as to the ideal type of insulin or mixture of insulin for subcutaneous injection. In general, mixtures of unmodified insulin and protamine zinc insulin have come into more widespread use. Results of extensive studies on such mixtures recently have been reported by Ulrich.<sup>37</sup> He studied blood sugar curves of a group of diabetic patients to whom were given on different days protamine zinc insulin alone, protamine zinc insulin and unmodified insulin in separate sites and protamine zinc insulin and unmodified insulin in mixtures containing various proportions of each type. Curves were obtained from these patients when they were in the fasting state and when they were fed the usual three meals during the day. In each instance the same total dose of insulin, 40 units, was given. The blood sugar curves obtained in this series of experiments showed that mixtures of the two types of insulin produced a less immediate hypoglycemic effect than did regular insulin injected separately but a greater immediate effect than did protamine zinc insulin given alone. The mixtures produced a more uniform and a more readily predictable action throughout the day than did the two types of insulin given in separate sites; a mixture of 1 part of unmodified insulin with 2 parts of protamine zinc insulin gave the best results. In such mixtures, the author suggested, regular insulin was loosely combined with protamine zinc insulin.

Recently Johlin<sup>38</sup> reported that the subcutaneous injection in experimental animals of a suspension in physiologic solution of sodium chloride of the precipitate formed when crystalline zinc insulin is shaken

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33. Hanzlik, P. J., and Cutting, W. C.: Agents Promoting Gastrointestinal Absorption of Insulin, *Endocrinology* **28**:368-374 (March) 1941.

34. Cutting, W. C., and Robson, G. B.: Clinical Trials with Insulin-Quinine Mixtures by Mouth in Diabetics, *Endocrinology* **28**:375-377 (March) 1941.

35. Driver, R. L., and Murlin, J. R.: Factors in Absorption of Insulin from the Alimentary Tract, *Am. J. Physiol.* **132**:281-292 (Feb.) 1941.

36. Cutting, W. C.; Morton, M. C., and Cohn, R. B.: Subcutaneous Administration of Insulin by Pellets, *Endocrinology* **28**:679-680 (April) 1941.

37. Ulrich, H.: Clinical Experiments with Mixtures of Standard and Protamine Zinc Insulins, *Ann. Int. Med.* **14**:1166-1179 (Jan.) 1941.

38. Johlin, J. M.: The Attenuation of Insulin by Adsorption, *Endocrinology* **29**:574-576 (Oct.) 1941.

for several hours with pure chloroform resulted in a reduced but prolonged hypoglycemic action, similar to that produced by other insoluble insulin preparations, such as protamine zinc insulin. This preparation has not been used clinically.

The question of the patient's resistance to insulin has been reviewed by several authors (Martin and associates,<sup>39</sup> Hart and Vicens<sup>40</sup>). In most of the cases reported, resistance to large doses of insulin was found in association with urticarial lesions. They recommended that massive doses of insulin be administered until the period of resistance has been overcome.

*Diabetic Coma.*—Mirsky and his collaborators<sup>41</sup> asserted that an excessive intake of carbohydrates will not accelerate the production of acetone bodies and thereby induce diabetic coma. They stated that acetone bodies are formed as the result of depletion of the glycogen reserves of the liver; in depancreatized dogs the administration of large amounts of dextrose, even in the absence of injected insulin, will cause the production of acetone bodies to cease. Likewise, in a group of patients who had severe diabetes mellitus and who received only enough insulin to prevent the development of a precoma state, the feeding of large amounts of carbohydrates (as much as 1,000 Gm. daily) markedly reduced the ketonuria which was present. According to the opinion expressed by these investigators, deprivation of insulin was the most important factor in the development of acidosis.

On the other hand, Cole<sup>42</sup> found that in 13 episodes of coma which occurred among 24 young diabetic patients acute infectious processes had been responsible in 9 instances and failure to take insulin in only 4 instances.

Duncan<sup>43</sup> has contributed an excellent review of the therapeutic measures to be employed in diabetic coma. He expressed a preference for the administration of both protamine zinc insulin and regular insulin at the start of treatment, to be followed every hour thereafter by the administration of 20 to 30 units of the regular type until the carbon

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39. Martin, W. P.; Martin, H. E.; Lyster, R. W., and Strouse, S.: Insulin Resistance: Critical Survey of the Literature with the Report of a Case, *J. Clin. Endocrinol.* **1**:387-398 (May) 1941.

40. Hart, J. F., and Vicens, C. A.: Association of Extreme Insulin Resistance with Allergy: Report of a Case, *J. Clin. Endocrinol.* **1**:399-401 (May) 1941.

41. Mirsky, I. A.; Franzblau, A. N.; Nelson, N., and Nelson, W. E.: Diabetes Mellitus: The Role of Excessive Carbohydrate Intake in the Etiology of Diabetic Coma, *J. Clin. Endocrinol.* **1**:307-313 (April) 1941.

42. Cole, L.: Diabetic Coma in a Series of Young Diabetics, *Brit. M. J.* **1**:882-884 (June 14) 1941.

43. Duncan, G. G.: Diabetic Coma (Ketosis), *Pennsylvania M. J.* **44**:725-727 (March) 1941.

dioxide-combining power of the blood increases to more than 30 volumes per cent. He administered sodium lactate intravenously to patients whose carbon dioxide-combining power either was low at the onset or did not increase after a suitable period of treatment. Krarup<sup>44</sup> reported that anuria and uremia in the presence of diabetic coma result from a deficiency in the fixed base; consequently, he recommended the intravenous administration of solutions of sodium bicarbonate as a means of restoration of renal function to normal.

*Diabetes and Surgical Operations.*—Close cooperation between internist and surgeon has made almost any type of surgical procedure as safe for the diabetic patient as it is for the nondiabetic patient. Recent extensive reviews of the subject of operation on the diabetic patient have been presented by Tyler<sup>45</sup> and Bothe.<sup>46</sup> Both of these authors emphasized the importance of careful preoperative preparation of the diabetic patient. When operation is urgent, the only preparation possible may be vigorous therapy directed toward reduction of acidosis, if it is present. The adequate intravenous administration of fluids, including solutions of dextrose, and insulin therapy were recommended. Delay of the operation, when this was possible, until such time as both hyperglycemia and glycosuria had been controlled and the hepatic stores of glycogen had been replenished, with the feeding of added carbohydrates, yielded optimal results. Both authors, however, agreed that early intervention in cases complicated by an infectious process was desirable, not only for relief of the local condition but for more rapid control of the diabetes. They stated that either spinal or local anesthesia was preferable to general anesthesia, the latter of which would tend further to deplete hepatic stores of glycogen and thus increase the likelihood of acidosis. Bothe reported that in a group of 14,000 diabetic patients of all ages who underwent many types of surgical procedures the mortality rate amounted to only 5 per cent.

Erb<sup>47</sup> advised the more frequent employment of conservative procedures rather than radical amputation in the presence of gangrene of the extremities among diabetic patients. Bothe expressed the opinion that for 40 per cent of such patients limited measures, such as incision and drainage or amputation of one digit, would suffice. In Erb's series

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44. Krarup, N. B.: Alkali Treatment in Diabetic Coma with Hyperazotemia and Anuria, *Ugesk. f. læger* **102**:27, 1940; abstracted, *J. Clin. Endocrinol.* **1**:630 (July) 1941.

45. Tyler, G. T., Jr.: Surgery in Diabetes, *South. Med. & Surg.* **103**:6-8 (Jan.) 1941.

46. Bothe, F. A.: The Surgical Diabetic, *Pennsylvania M. J.* **44**:1018-1021 (May) 1941.

47. Erb, W. H.: Conservative Surgery in Diabetic Gangrene, *Pennsylvania M. J.* **44**:1131-1134 (June) 1941.

local procedures saved the limb in 50 per cent of patients. However, both writers agreed that conservative therapy is to be attempted only for those patients whose vessels (in the extremities) are competent. In the presence of severe degrees of arteriosclerosis, radical amputation to as far as the zone of adequate circulation was called the procedure of choice. In a recent review in *The Journal of the American Medical Association* <sup>48</sup> the indications for each type of amputation for diabetic gangrene were described. In general, the indications given for radical amputation were septicemia secondary to the gangrene, rapidly extending infections and extensive sepsis in a debilitated patient.

*Diabetes and Pregnancy.*—Little has been added to this subject since the writing of last year's review. White <sup>49</sup> and Smith and Smith <sup>50</sup> have reviewed their experience with the toxemias of pregnancy both among diabetic and among nondiabetic patients and have concluded that the elevated value for chorionic gonadotropin in the serum of such patients is due to disturbed metabolism of estrogen involving greater and more rapid destruction of this hormone. White's suggestion that hormonal imbalance is responsible for the toxemias of pregnancy and that replacement therapy with progestin and estrogen is indicated has been criticized by Hurwitz.<sup>51</sup> He stated that her work had been inadequately controlled and that accidents of pregnancy also occurred among diabetic women who had a normal hormonal balance. He added that he had been able to obtain as good results in his series without substitution therapy as did White in her series of treated patients. White <sup>49</sup> and Joslin <sup>52</sup> replied that they had not felt justified in increasing their series of untreated patients, since the fetal survival rate in this group was less than half that in the treated group.

Hurwitz also denied that routine cesarian section was advisable for pregnant diabetic women. He reported a fetal mortality rate of 15 per cent among 53 diabetic women who were allowed to give birth to their infants spontaneously, a rate which compared favorably with that given by White and her associates for their treated patients. Porter <sup>53</sup> and Nothmann,<sup>54</sup> however, reported that fetal hypoglycemia, caused by

48. Amputation in Diabetes Mellitus and Peripheral Vascular Disease, Council on Physical Therapy, J. A. M. A. **117**:1095-1097 (Sept. 27) 1941.

49. White, P.: Reply to Hurwitz, J. A. M. A. **116**:645 (Feb. 15) 1941.

50. Smith, G. V., and Smith, O. W.: Estrogen and Progestin Metabolism in Pregnancy: II. The Endocrine Inbalance of Preeclampsia and Eclampsia; Summary of Findings to February, 1941, J. Clin. Endocrinol. **1**:470-476 (June) 1941.

51. Hurwitz, D.: Pregnancy Accidents in Diabetes, J. A. M. A. **116**:645 (Feb. 15) 1941.

52. Joslin, E. P.: Reply to Hurwitz, J. A. M. A. **116**:645-646 (Feb. 15) 1941.

53. Porter, R. D.: Management of Pregnancy in Diabetes, Pennsylvania M. J. **44**:1011-1013 (May) 1941.

54. Nothmann, M.: Diabetes Mellitus and Pregnancy, New England J. Med. **224**:275-280 (Feb. 13) 1941.



hypertrophy of the islets of Langerhans in the infant, occurred so frequently that section during the latter part of the ninth month of pregnancy is indicated. Potter and co-workers<sup>55</sup> reviewed the observations made at necropsy on the pancreases of 26 infants whose mothers had diabetes, of 3 infants whose mothers seemed questionably to have diabetes and of 16 infants whose mothers did not have diabetes. They concluded that an increase in fetal islet tissue may be found either in the presence or in the absence of abnormal sugar metabolism in the mother and that there is no correlation either between the severity or the degree of control of diabetes in the mother and the increase in the islet tissue or between the amount of islet tissue found at necropsy and the infant's blood sugar level prior to death.

*Miscellaneous Complications.*—Lamb and Keltz<sup>56</sup> reviewed the dermatologic complications of diabetes mellitus; they concluded that control of the diabetes is the most important therapeutic measure under such circumstances.

McKee<sup>57</sup> found that among 2,360 diabetic patients on whom fundoscopic examination was done there were 476 (21.7 per cent) who exhibited retinal changes which could be "more or less" related to their diabetes; 8.6 per cent of these 476 patients exhibited typical diabetic retinitis, and 43 per cent exhibited retinal arteriosclerosis. There was only 1 instance of lipaemia retinalis in the entire group.

A syndrome which has been recognized recently in association with diabetes mellitus is that of so-called intercapillary glomerulosclerosis. This was first described in 1936 by Kimmelstiel and Wilson,<sup>58</sup> who reported that among patients who had presented a picture of diabetes mellitus (usually of long duration), edema of the nephrotic type, gross albuminuria and varying degrees of hypertension, postmortem examination of the kidneys disclosed a characteristic deposition of hyaline material between the capillaries of the glomerular tufts. Porter and Walker<sup>59</sup> recently reviewed this subject and reported that in addition to those clinical features mentioned by Kimmelstiel and Wilson, 100 per cent of their patients had retinal changes associated with arteriosclerosis,

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55. Potter, E. L.; Seckel, H. P. G., and Stryker, W. A.: Hypertrophy and Hyperplasia of Islets of Langerhans of the Fetus and of the Newborn Infant; *Arch. Path.* **31**:467-482 (April) 1941.

56. Lamb, J. H., and Keltz, B. F.: Skin Manifestations in Diabetes Mellitus, *J. Oklahoma M. A.* **34**:93-97 (March) 1941.

57. McKee, S. H.: Examination of Fundus in 2,360 Diabetics, *Canad. M. A. J.* **45**:127-129 (Aug.) 1941.

58. Kimmelstiel, P., and Wilson, C.: Intercapillary Lesions in the Glomeruli of the Kidney, *Am. J. Path.* **12**:83-98 (Jan.) 1936.

59. Porter, W. B., and Walker, H.: The Clinical Syndrome Associated with Intercapillary Glomerulosclerosis, *J. A. M. A.* **116**:459-463 (Feb. 8) 1941.

whereas 50 per cent of them had the punctate hemorrhages and exudates characteristic of diabetic retinitis. They outlined the sequence of events under such circumstances as follows: (1) mild diabetes occurring in a patient past 40 years of age; (2) the appearance, usually within the next three years, of albuminuria, mild edema and hypoproteinemia and arteriosclerosis; (3) exaggeration of the symptoms and the development of hypertension within the next five years, and (4) death a few months later of the renal and vascular complications. The authors suggested that arterial and arteriolar degeneration perhaps was the underlying factor in the entire syndrome, including the diabetes.

Siegel and Allen<sup>60</sup> found these renal lesions among 33.3 per cent of 105 diabetic patients on whom necropsy was performed. The retinitis of diabetes was found among all the patients who had presented nephrotic symptoms. The authors expressed the belief that the diabetic lesion could be easily distinguished microscopically from glomerulosclerotic and nephrosclerotic lesions among nondiabetic patients and that the lesion was a focal intramural type of glomerulosclerosis arising within the capillary walls rather than between these walls, as has been previously reported.

Several authorities<sup>61</sup> have recorded the frequency of disease of the gallbladder among diabetic patients. Rhodes<sup>62</sup> and Thomason,<sup>63</sup> however, reported that acute pancreatitis or pancreatic lithiasis rarely terminates in diabetes mellitus.

#### SPONTANEOUS HYPOGLYCEMIA

Additional reports of spontaneous hypoglycemia continue to appear in the literature. Waddell and Humphries<sup>64</sup> concluded that this condition was not uncommon, since they encountered 6 instances of it among children within two and a half years. Sandler<sup>65</sup> stated: "Chronic hypoglycemia is a common disorder masquerading as pseudoulcer, chronic appendicitis, abdominal migraine, neuro-circulatory asthenia, etc." He reported on 6 patients who had undergone one or more major abdominal

60. Siegel, S., and Allen, A. C.: Intercapillary Glomerulosclerosis (Kimmelstiel-Wilson) and Nephrotic Syndrome in Diabetes Mellitus, *Am. J. M. Sc.* **201**:516-528 (April) 1941.

61. Zisserman.<sup>24</sup> Dry and Tessmer.<sup>25</sup> Tyler.<sup>45</sup>

62. Rhodes, G. K.: Acute Pancreatitis: Thirty-Five Cases with Observations on Blood Amylase Studies, *West. J. Surg.* **49**:266-270 (May) 1941.

63. Thomason, T. H.: Pancreatic Lithiasis with Diabetics: Report of Four Cases, *South. Surgeon* **10**:135-143 (Feb.) 1941.

64. Waddell, W. W., Jr., and Humphries, T. J.: Spontaneous Hypoglycemia in Childhood, *Virginia M. Monthly* **68**:440-448 (Aug.) 1941.

65. Sandler, B. P.: Chronic Abdominal Pain Due to Hypoglycemia with Note on Pathogenesis of Neurotic Symptomatology, *Surgery* **9**:331-348 (March) 1941.

operations, without relief, for recurrent episodes of abdominal pain. Additional inquiry into their histories revealed in each instance that pain was associated with symptoms of hypoglycemia (sweating, faintness, dizziness and the like); all were relieved of their symptoms when they subsisted on a low carbohydrate, high protein diet. None of these patients underwent surgical exploration for pancreatic tumor.

Allen<sup>66</sup> has stated that in most cases hyperinsulinism is mild and that it represents a disorderly rather than an excessive secretion of insulin; he expressed the belief, therefore, that the condition should be termed "dysinsulinism" rather than "hyperinsulinism." He doubted that small islet cell tumors could flood the body with as much insulin as would be required to produce the symptoms encountered among these patients, because epinephrine will prevent attacks. He doubted that this drug could serve as an antidote to a large excess of insulin by releasing dextrose from the liver. Furthermore, high protein diets have been reported to prevent attacks, and no person could eat enough protein to protect against a large excess of insulin. Either a single large dose or repeated small excessive doses of insulin ultimately result in toxicity, with nausea, vomiting and prostration, not relieved by the administration of dextrose, but these symptoms were not seen among patients who had spontaneous hypoglycemia. For these reasons, he did not advise routine surgical exploration of the pancreas in these patients; instead, he recommended high carbohydrate diets, which could be made to contain relatively few calories if the patient became greatly overweight.

On the other hand, several recently reported instances of spontaneous hypoglycemia associated with proved (at surgical exploration or necropsy) islet cell tumors have brought the number of recorded cases of this syndrome to considerably more than 100.<sup>67</sup> In most instances removal of the pancreatic tumor was followed by cessation of the attacks of hypoglycemia. Indeed, Rowntree<sup>68</sup> and Windfeld<sup>69</sup> recommended surgical exploration of the pancreas for all patients who presented proved

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66. Allen, F. M.: Hyperinsulinism: Spontaneous and Artificial Hyperinsulinism, *J. Clin. Endocrinol.* **1**:595-603 (July) 1941.

67. Frantz, V. K.: Tumors of Islets of Langerhans with Hyperinsulinism, *New York State J. Med.* **41**:881-882 (April 15) 1941. Brunschwig, A.: Large Islet-Cell Tumor of Pancreas, *Surgery* **9**:554-560 (April) 1941. Flinn, L. B.; Beatty, G. A.; Ginsberg, M., and Hemsath, F. A.: Carcinoma of the Islands of Langerhans, with Hypoglycemia and Metastasis of the Liver, *J. A. M. A.* **117**:283-285 (July 26) 1941. Meyer, K. A.; Amtman, L., and Perlman, L.: Islet Cell Tumor of the Pancreas: Report of Case, *ibid.* **117**:16-20 (July 5) 1941.

68. Rowntree, L. G.: Hyperinsulinism, *J. M. Soc. New Jersey* **38**:301-305 (June) 1941.

69. Windfeld, P.: Surgical Treatment of Pancreas Adenomas Producing Insulin (Insulinomas), *Ugesk. f. læger* **103**:353 (March 20) 1941; abstracted, *J. A. M. A.* **117**:972 (Sept. 13) 1941.

hypoglycemia. Rowntree reported that subtotal pancreatectomy was beneficial for patients in whom no tumor was found. Windfeld, however, expressed the opposite view. Burtness and associates<sup>70</sup> reported that a probable diagnosis of pancreatic tumor is indicated for those patients among whom results of the test for tolerance to insulin show only slight sensitivity to insulin, that is, when the value for blood sugar decreases little throughout the test and then slowly returns to normal.

Malignant changes in islet cell tumors have been reported relatively often; such changes occurred in 21 of 96 cases found in the literature by Frantz. Flinn and his associates, however, found only 4 instances of metastasizing pancreatic islet tumors in the literature and reported a fifth case.

#### OBESITY

Bauer<sup>71</sup> reviewed the subject of obesity and concluded:

Obesity is a compulsory tendency toward marked overweight due to abnormal accumulation of fat by persons who are left alone to their automatic regulation and are not supervised as far as the intake of food and expenditure of energy are concerned.

Such a condition he related to an abnormal gene complex, rather than to simple caloric excesses in the diet. He agreed, however, that a submaintenance diet was the only practical form of therapy for these patients.

Bruch<sup>72</sup> warned against the treatment of obesity with glandular preparations, particularly among children. Short<sup>73</sup> reported a case in which a 35 year old woman lost 300 pounds (about 136 Kg.) in eighteen months when she was maintained on a 600 to 800 calory diet. Her basal metabolic rate, which had been elevated, and her dextrose tolerance curve, which had been of the diabetic type, both returned to normal after the reduction in weight.

Handelsman and Gordon<sup>74</sup> reported that patients in whom obesity and true hypothyroidism coexist are rare; the majority of obese patients, he stated, could receive large doses of thyroid for short intervals with

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70. Burtness, H. I.; Koehler, A. E., and Saint, J. H.: Hyperinsulinism Due to Adenoma of Islets of Langerhans: Case Report with Metabolic Studies Before and After Removal of Tumor, *Ann. Int. Med.* **14**:1915-1932 (April) 1941.

71. Bauer, J.: Obesity: Its Pathogenesis, Etiology, and Treatment, *Arch. Int. Med.* **67**:968-994 (May) 1941.

72. Bruch, H.: Obesity in Childhood and Endocrine Treatment, *J. Pediat.* **18**:36-56 (Jan.) 1941.

73. Short, J. J.: Rapid Weight Reductions: Loss of Three Hundred Pounds in Eighteen Months; Report of a Case, *J. A. M. A.* **117**:506-510 (Aug. 16) 1941.

74. Handelsman, M. B., and Gordon, M. B.: Obesity: The Calorigenic Action of Thyroid Substance in Obese Patients, *J. Clin. Endocrinol.* **1**:612-619 (July) 1941.

relatively slight or no calorogenic effect. Andersen,<sup>75</sup> however, reported on 3 patients in all of whom severe thyrotoxicosis and auricular fibrillation developed after the administration of large amounts of thyroid for obesity. Bram<sup>76</sup> reported 54 instances in which exophthalmic goiter had followed drastic reduction of weight and stated that this sequel was particularly likely to develop among those patients who took thyroid along with the diet.

#### THYROID GLAND

McClendon and Foster<sup>77</sup> determined the content of thyroxin iodine in the blood of 373 patients and reported that for every microgram of thyroxin iodine in 100 cc. of whole blood there was about 1 mg. of thyroxin in the body of an adult person weighing 65 Kg. Their figures showed that a direct relation existed between the micrograms of thyroxin iodine in 100 cc. of whole blood and the patient's basal metabolic rate. Consequently, they expressed the belief that such determinations could be used as a check on the reliability of any individual basal metabolic rate, or even as a substitute for the basal metabolic rate. They cautioned, however, that the previous use of either yellow mercurous iodide or radiopaque oil (iodized poppyseed oil) would lead to errors in determination of iodine in the blood.

Dunlap<sup>78</sup> presented an extensive review of the states associated with low basal metabolic rate. He classified them as "primary hypothyroidism" myxedema or cretinism, and "secondary hypothyroidism," hypometabolism without myxedema. The latter classification included the majority of patients found to have low basal metabolic rates. Although the cause of primary hypothyroidism is, of course, deficient secretion by the thyroid gland, the underlying factor in the secondary type of hypothyroidism has been less well understood. Pituitary deficiency conceivably might play a role. Some types of secondary hypothyroidism respond well to replacement therapy with thyroid. Among these the author included such conditions as menstrual disturbances not related to pelvic disease,<sup>79</sup> sterility, habitual abortion, anorexia nervosa

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75. Andersen, W. T.: Three Cases of Hyperthyroidism After Weight-Reducing Thyroidin Treatment, *Acta med. Scandinav.* **104**:589-598, 1940.

76. Bram, I.: Weight Reduction as an Exciting Cause of Exophthalmic Goiter, *M. Rec.* **152**:437-439 (Dec. 18) 1940.

77. McClendon, J. F., and Foster, W. C.: Thyroid Hormone in the Blood and Tissues in Relation to Basal Metabolic Rate, *Endocrinology* **28**:412-418 (March) 1941.

78. Dunlap, H. F.: The Clinical Significance and Treatment of States Associated with Low Basal Metabolic Rates, *J. Indiana M. A.* **34**:73-77 (Feb.) 1941.

79. Haines, S. F., and Mussey, R. D.: Certain Menstrual Disturbances Associated with Low Basal Metabolic Rates Without Myxedema, *J. A. M. A.* **105**:557-560 (Aug. 24) 1935.

and certain other nutritional disturbances. Usually, increase in the basal metabolism required the administration of large doses of thyroid.

Hertz and Galli-Mainini<sup>80</sup> reported that overgrowth was a constant observation among 121 juvenile patients who had thyrotoxicosis and that the overgrowth appeared to coincide with the normal peaks of growth. They suggested that excessive secretion by the thyroid gland might have acted as a synergist to the growth factor of the anterior lobe of the pituitary and that, therefore, thyroid might be useful in the treatment of persons whose height is less than normal. On the other hand, Beard<sup>81</sup> reported that the simultaneous administration of desiccated thyroid and anterior pituitary extract containing the growth factor to a cretin 16 years old produced no more growth than could be obtained by administration of the thyroid alone.

Cutler and Hoerr<sup>82</sup> have reported results of a five year follow-up study of 57 patients with cardiac disease who underwent total thyroidectomy. They concluded that for a selected group of patients suffering from angina pectoris, excluding those with evidence of congestive heart failure or cardiac enlargement, the operation offered considerable hope of relief of symptoms. Berlin and associates,<sup>83</sup> in a similar review of seven and a half years' experience with total thyroidectomy for chronic cardiac disease, concluded that this procedure was beneficial to "a certain group of patients for whom life was quite intolerable before operation because of complete invalidism due to congestive failure or severe repeated attacks of excruciating chest pain at bed rest or on slight exertion."

#### ADRENAL CORTEX

Several comprehensive reviews of the progress which has been made in the treatment of adrenal cortical insufficiency recently have appeared.<sup>84</sup>

80. Hertz, S., and Galli-Mainini, C.: Effect of Thyroid Hormone on Growth in Thyrotoxic and Myxedematous Children and Adolescents, *J. Clin. Endocrinol.* **1**:518-522 (June) 1941.

81. Beard, E. E.: Cretinism: Lack of Response to Anterior Pituitary Growth Principle, *J. Clin. Endocrinol.* **1**:293-296 (April) 1941.

82. Cutler, E. C., and Hoerr, S. O.: Total Thyroidectomy for Heart Disease: A Five Year Follow-Up Study, *Ann. Surg.* **113**:245-259 (Feb.) 1941.

83. Berlin, D. D.; Riseman, J. E. F., and Blumgart, H. L.: The Present Status of Total Thyroidectomy: A Review of Seven and One-Half Years' Experience, *Tr. Am. A. Study Goiter*, 1940, pp. 1-6.

84. (a) Loeb, R. F.: Adrenal Cortex Insufficiency, *J. A. M. A.* **116**:2495-2500 (May 31) 1941. (b) Thorn, G. W.: Treatment of Addison's Disease, *J. Clin. Endocrinol.* **1**:76-81 (Jan.) 1941. (c) Hampton, H. P., and Kepler, E. J.: Addison's Disease: Treatment and Prognosis, *Am. J. M. Sc.* **202**:264-271 (Aug.) 1941. (d) McGavack, T. H.: Adrenal Insufficiency: Some Pitfalls in the Treatment of Addison's Disease, *J. Clin. Endocrinol.* **1**:68-75 (Jan.) 1941. (e) Kepler, E. J., and Willson, D. M.: Diseases of the Adrenal Glands: I. Addison's Disease, *Arch. Int. Med.* **68**:979-1009 (Nov.) 1941.

Desoxycorticosterone acetate in oil injected intramuscularly has largely supplanted other replacement therapy in the treatment of Addison's disease. Most authors have recommended that the drug be given in amounts ranging from 2 to 5 mg. per day. In association with the synthetic compounds, administration of 2 to 5 Gm. of extra sodium chloride plus the ingestion of a liberal diet, which may be a general, high vitamin, high calory diet, a high protein diet or a high carbohydrate diet, has been employed. The pitfalls of treatment with desoxycorticosterone acetate, however, have been reemphasized by McGavack.<sup>84d</sup> He warned that the appearance of edema of the extremities, rapid gain in weight, increase in blood pressure and, finally, cardiac and circulatory embarrassment, are indications that the dosage of the drug or of the extra salt or perhaps of both is excessive. Willson, Dry and one of us (E. H. R.)<sup>85</sup> recently reported an instance of cardiac failure after the treatment of Addison's disease with desoxycorticosterone acetate, a report which well illustrates the potential dangers involved in the use of this drug. Most authorities have reported that administration of the aqueous extract of the whole cortex is still the most effective treatment of crises of adrenal insufficiency. Furthermore, it should be emphasized that for a certain small group of patients who have Addison's disease the synthetic preparation has proved to be ineffective; these patients often do well when they are treated with the whole cortical extract.

Britton and Kline<sup>86</sup> reported that desoxycorticosterone acetate acted too slowly in adrenalectomized cats to be effective in the immediate treatment of severe degrees of adrenal insufficiency. In addition, both these authors and others<sup>87</sup> have found the synthetic preparation to be much less effective in restoration of values for blood sugar and for glycogen in the liver to normal than is whole cortical extract.

In 1940 Anderson and his associates<sup>88</sup> reported the successful treatment of 6 patients suffering from Addison's disease by means of the sublingual administration of 2 to 6 mg. of desoxycorticosterone acetate dissolved in propylene glycol and given in divided doses. Turnoff and Rowntree<sup>89</sup> recently reported that 2 patients who had advanced adrenal

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85. Willson, D. M.; Rynearson, E. H., and Dry, T. J.: Cardiac Failure Following Treatment of Addison's Disease with Desoxycorticosterone Acetate, *Proc. Staff Meet., Mayo Clin.* **16**:168-173 (March 12) 1941.

86. Britton, S. W., and Kline, R. F.: Relative Effects of Desoxycorticosterone and Whole Corticoadrenal Extract on Adrenal Insufficiency, *Am. J. Physiol.* **133**: 503-510 (July) 1941.

87. Cleghorn, R. A.; Fowler, J. L. A.; Wenzel, J. S., and Clarke, A. P. W.: The Desoxycorticosterone Acetate Requirement of the Adrenalectomized Dog, *Endocrinology* **29**:535-544 (Oct.) 1941. McGavack.<sup>84d</sup>

88. Anderson, E.; Haymaker, W., and Henderson, E.: Successful Sublingual Therapy in Addison's Disease, *J. A. M. A.* **115**:2167-2168 (Dec. 21) 1940.

89. Turnoff, D., and Rowntree, L. G.: Successful Sublingual Therapy in Addison's Disease: A Confirmative Report, *J. A. M. A.* **116**:2016 (May 3) 1941.

insufficiency were satisfactorily maintained on 1 mg. of the drug dissolved in propylene glycol, taken six to seven times daily. The patients were directed to hold the drug under the tongue for fifteen minutes and then to expectorate it. Sodium chloride was not added to their diet. Not all investigators, however, have found the oral route to be as effective as the intramuscular route in the administration of the drug. Thompson<sup>90</sup> reported that when desoxycorticosterone acetate was given orally it was only about 20 per cent as effective as it is when it is given by injection. Despite these contrary reports, it is probable that the convenience of a preparation to be used orally will lead to extensive employment of it, particularly when improved methods of synthesis of the drug make it available in larger amounts.

The subcutaneous implantation of pellets containing the synthetic substance was reported<sup>91</sup> to have been successful at about the same time that reports of the effective oral administration of the drug appeared in the literature. Patients who have been successfully treated in this manner have been stabilized first by the daily injection of the synthetic compound in oil. Wilder<sup>92</sup> has stated that the period of stabilization should extend over at least six months. When the daily maintenance dose has been determined, the amount of the drug calculated to be sufficient to maintain the patient for several months is implanted in several pellets beneath the skin. Thorn and associates<sup>93</sup> have given a method for the determination of the number and content of the pellets which will permit absorption at the desired rate. Edema among the patients has been controlled by reduction of their intake of salt.

In final consideration of the treatment of Addison's disease with desoxycorticosterone acetate by whatever route of administration, it should be emphasized that this drug represents only one of the fractions contained in the whole cortical extract. Its administration does not, therefore, constitute complete replacement therapy, and therein lies the explanation of its failure to benefit all patients who have adrenal insufficiency. Not until either a much more potent whole cortical extract

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90. Thompson, W. O., discussion on Thorn.<sup>84b</sup>

91. Billmann, F., and Grathwohl, F. D.: Efficacy of Subcutaneous Implantation of Tablets of Crystalline Desoxycorticosterone Acetate on Bilaterally Adrenalectomized Dogs, *Klin. Wchnschr.* **19**:1030-1033 (Oct. 5) 1940. Moehlig, R. C.: Addison's Disease Treated by Implantation of Desoxycorticosterone Acetate Pellets, *Endocrinology* **27**:633-637 (Oct.) 1940. Segall, G.: Treatment of Addison's Disease with Pellets of Synthetic Desoxycorticosterone Acetate Implanted Subcutaneously, *Am. J. M. Sc.* **201**:202-208 (Feb.) 1941.

92. Wilder, R. M., in discussion on Thorn.<sup>84b</sup>

93. Thorn, G. W.; Howard, R. P.; Emerson, K., Jr., and Firor, W. M.: Treatment of Addison's Disease with Pellets of Crystalline Adrenal Cortical Hormone (Synthetic Desoxycorticosterone Acetate) Implanted Subcutaneously, *Bull. Johns Hopkins Hosp.* **64**:339-365 (May) 1939.



or adequate amounts of each of the individual compounds elaborated by the adrenal cortex are available will entirely satisfactory results be obtained for these patients.

The treatment of patients who have Addison's disease by means of grafts of the adrenal gland has been reported in 5 cases, according to Katz and Mainzer.<sup>94</sup> They added a sixth instance to the literature. An adrenal gland from a patient who had just died of a cerebral neoplasm was grafted into the abdominal muscles of a patient who had advanced adrenal insufficiency. After the latter patient had recovered from the immediate effects of the operation, his blood pressure was maintained and his general condition was excellent for a period of fifteen months of observation.

The role of the adrenal glands in relation to shock has been subjected to considerable scrutiny. Swingle and associates<sup>95</sup> reported that desoxycorticosterone acetate would protect adrenalectomized dogs against traumatic shock. They suggested that the normal adrenal cortex was necessary in some way for the maintenance of the normal ability of the periphery to cope with vascular strain. Rhoads and co-workers<sup>96</sup> reported that the intravenous administration of cortical extract to patients who had extensive burns reduced the amount of blood plasma which was required to restore the circulation to normal, presumably by reducing the amount of plasma protein which escaped through the capillaries into the interstitial fluid. They suggested that capillary permeability might have been altered by the cortical extract. Besser,<sup>97</sup> however, reported that the preoperative administration of 5 to 10 mg. of desoxycorticosterone acetate, in three separate doses twelve, six and four hours prior to surgical operation, did not reduce the incidence of surgical shock. He said that 31 per cent of 72 patients so treated exhibited shock, as evidenced by systolic blood pressures of less than 80 mm. of mercury and diastolic blood pressures of less than 60 mm. of mercury, as compared with 39 per cent of 68 untreated patients in whom postoperative shock likewise developed.

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94. Katz, F., and Mainzer, F.: Successful Grafting of Adrenal Gland in a Case of Addison's Disease, *Brit. M. J.* **1**:617-618 (April 26) 1941.

95. Swingle, W. W.; Hays, H. W.; Remington, J. W.; Collings, W. D., and Parkins, W. M.: The Effect of Priming Doses of Desoxycorticosterone Acetate in Preventing Circulatory Failure and Shock in Adrenalectomized Dogs, *Am. J. Physiol.* **132**:249-258 (Feb.) 1941.

96. Rhoads, J. E.; Wolff, W. A., and Lee, W. E.: Use of Adrenal Cortical Extract in the Treatment of Traumatic Shock of Burns, *Ann. Surg.* **113**:955-965 (June) 1941.

97. Besser, E. L.: Role of Adrenal Glands in Shock: Value of Desoxycorticosterone Acetate in the Prevention of Operative Shock, *Arch. Surg.* **43**:249-256 (Aug.) 1941.

A considerable amount of work has indicated that a close relation exists between the adrenal glands and the gonads. It has been known for some time that virilism in women, as seen in Cushing's syndrome, and pubertas praecox in children not infrequently are seen in association with tumors of the adrenal cortex. Mintz and Geist<sup>98</sup> have reported that the adrenal cortex is almost always involved in virilism in women. Albright and associates<sup>99</sup> stated that Cushing's syndrome, whatever the cause, is associated with hyperadrenocorticism.

Wintersteiner<sup>100</sup> reported that the urine of eunuchs and also that of ovariectomized women showed "small but definite amounts of androgenic activity." Hirschmann<sup>101</sup> identified the androgens excreted by ovariectomized women as androsterone and dehydroisoandrosterone. Wintersteiner expressed the belief that there was "a potential availability rather than an active functional secretion of androgens and estrogens from the adrenal cortex." He stated that this secretion did not play an important part functionally in the normal adult organism. Woolley and co-workers<sup>102</sup> reported that removal of the gonads of mice of either sex was followed by the development of hyperplastic adrenal cortical changes.

Emery and Gottsch<sup>103</sup> reported that either administration of progesterone (1 mg. or more daily) or the implantation of the pituitary glands of castrated rats will maintain adrenalectomized female rats. They expressed the belief that pituitary implantation stimulated the formation of corpora lutea, which in turn secreted increased amounts of progesterone. Estrogen not only was of no benefit in the maintenance of such rats but actually was harmful. Corey<sup>104</sup> confirmed the life-sustaining effects of progesterone in adrenalectomized male and pregnant or ovariectomized female rats. Progesterone could even bring

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98. Mintz, N., and Geist, S. H.: Adrenocortical Syndrome: The Adrenal Cortex and Its Relation to Virilism, *J. Clin. Endocrinol.* **1**:316-326 (April) 1941.

99. Albright, F.; Parson, W., and Bloomberg, E.: Therapy in Cushing's Syndrome: Cushing's Syndrome Interpreted as Hyperadrenocorticism Leading to Hypergluconeogenesis; Results of Treatment with Testosterone Propionate, *J. Clin. Endocrinol.* **1**:375-384 (May) 1941.

100. Wintersteiner, O.: The Adrenogenital Syndrome, *J. A. M. A.* **116**:2679-2683 (June 14) 1941.

101. Hirschmann, H.: Steroids of the Urine of Ovariectomized Women, *J. Biol. Chem.* **136**:483-502 (Nov.) 1940.

102. Woolley, G.; Fekete, E., and Little, C. C.: Effect of Castration in the Dilute Brown Strain of Mice, *Endocrinology* **28**:341-343 (Feb.) 1941.

103. Emery, F. E., and Gottsch, L. G.: Studies on Pituitary Implants and Extracts in Adrenalectomized Rats, *Endocrinology* **28**:321-324 (Feb.) 1941.

104. Corey, E. L.: Comparative Effects of Progesterone and Cortico-Adrenal Extracts on Normal Adrenalectomized and Other Animals, *Am. J. Physiol.* **132**:446-453 (March) 1941.

about recovery from acute insufficiency in these animals. This substance, however, did not have such beneficial effects in adrenalectomized nonpregnant female rats; the author postulated that in these animals the presence of estrogen might have prevented the effect. Smith and Smith<sup>105</sup> reported that among pregnant women suffering from toxemia whose hormonal balance had been found to be abnormal the administration of adrenal cortical extract had a beneficial effect, similar to that manifested by the administration of progesterone.

Since desoxycorticosterone acetate and progesterone have been shown to be closely related chemically, it might be supposed that the former would have an even greater progesterone-like effect than would the extract of the whole adrenal cortex. Indeed, in the treatment of adrenalectomized rats over a long period of adrenal insufficiency desoxycorticosterone acetate and progesterone have been reported to have similar life-sustaining effects. Selye and Dosne,<sup>106</sup> however, were unable to confirm these observations in experiments when acute adrenal sufficiency was present. Furthermore, Paschkis<sup>107</sup> has reported that desoxycorticosterone acetate had no androgenic activity in castrated rats or chicks, and Hamblen and his associates<sup>108</sup> reported that among 8 women, none of whom had Addison's disease, this drug neither increased the excretion of sodium pregnandiol glucuronide (the excretion product of progesterone) nor produced changes in the endometrium characteristic of a late degenerative phase of the menstrual cycle.

Stephens<sup>109</sup> reported on 2 patients whom he considered to have hypopituitarism and whose episodes of nausea, vomiting and low blood pressure represented, he concluded, adrenocortical insufficiency. In 1 of these patients a state of shock was precipitated by the administration of thyroid for myxedema. The symptoms of both these patients were relieved by the administration of extra sodium chloride. He advised that all patients suspected of having hypopituitarism who are to be operated on or who are to be given thyroid undergo a salt deprivation test for adrenal insufficiency as a precautionary measure.

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105. Smith, G. V., and Smith, O. W.: Effect of Hormone Administration in Pre-Eclampsia, *J. Clin. Endocrinol.* **1**:477-484 (June) 1941.

106. Selye, H., and Dosne, C.: Action of Desoxycorticosterone Acetate and Progesterone on Blood and Tissue Chlorides of Normal and Adrenalectomized Animals, *Am. J. Physiol.* **132**:522-528 (March) 1941.

107. Paschkis, K. E.: Androgenic Action of Desoxycorticosterone Acetate, *Proc. Soc. Exper. Biol. & Med.* **46**:336-338 (Feb.) 1941.

108. Hamblen, E. C.; Cuyler, W. K.; Pattee, C. J., and Axelson, G. J.: Studies of the Progesterone-Like Action of Desoxycorticosterone Acetate in Women, *Endocrinology* **28**:306-308 (Feb.) 1941.

109. Stephens, D. J.: Pituitary and Adrenocortical Insufficiency: The Use of Sodium Chloride in the Treatment of Hypopituitarism, *J. Clin. Endocrinol.* **1**:109-112 (Feb.) 1941.

## PITUITARY BODY

Sevringhaus<sup>110</sup> has considered in detail the dysfunctions of the anterior lobe of the pituitary body and the treatment of them. He concluded that only two of these conditions are susceptible to successful endocrine therapy at present, namely, dysfunction involving the "growth-promoting factor" and dysfunction involving the "gonadotropic factor."

Sutton<sup>111</sup> reported that among 6 patients who had pellagra, polyneuritis, cheilosis or other evidence of deficiency of the vitamin B complex, improvement or recovery followed the injection of extract of the anterior lobe of the pituitary body. Cessation of this treatment resulted in relapse. In some cases of pellagra with achylia, treatment with extract of the anterior lobe of the pituitary body brought about a return of the secretion of hydrochloric acid in the stomach. Some of the patients suffering from pellagra who responded to therapy with extract of the anterior lobe of the pituitary body previously had failed to respond to the administration of nicotinic acid, riboflavin and liver substance (given parenterally) and the ingestion of an adequate diet. The author thought it possible that the hormone (or hormones) of the anterior lobe of the pituitary body was essential to utilization of the vitamin B complex.

The successful treatment of diabetes insipidus by the intramuscular administration of pitressin tannate in oil has been reported by Thorn and Stein.<sup>112</sup> The polyuria and polydipsia of 3 patients who received this type of therapy were controlled twenty-four to forty-eight hours by a single injection. The authors warned that excessive doses of pitressin tannate would result in retention of sodium chloride and water.

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110. Sevringhaus, E. L.: Dysfunctions of the Anterior Lobe of the Pituitary and Their Treatment, *J. A. M. A.* **116**:221-225 (Jan. 18) 1941.

111. Sutton, D. C.: Interrelation Between the Vitamin B Complex and the Anterior Lobe of the Pituitary Gland, *South. M. J.* **34**:47-51 (Jan.) 1941.

112. Thorn, G. W., and Stein, K. E.: Pitressin Tannate Therapy in Diabetes Insipidus, *J. Clin. Endocrinol.* **1**:680-687 (Aug.) 1941.

## News and Comment

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**American Association of Industrial Physicians and Surgeons and American Industrial Hygiene Association.**—The American Association of Industrial Physicians and Surgeons and the American Industrial Hygiene Association will hold their joint annual convention in Cincinnati April 13 to 17, 1942. Medical and hygienic problems associated with the present huge task of American industry will be presented and discussed in clinics, lectures, symposiums and scientific exhibits. The meeting will provide a five day institute for the interchange and dissemination of information on new problems, as well as for the consideration of up-to-date methods of dealing with those that are well known. The industrial physicians have taken responsibility for the program of the first two and one-half days and the hygienists for that of the remaining two and one-half days, but most of the subjects chosen for discussion will be of interest not only to physicians but to industrial engineers and executives.

## Book Reviews

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**Body Mechanics in Health and Disease.** By J. E. Goldthwait, M.D.; L. T. Brown, M.D.; L. T. Swaim, M.D.; J. G. Kuhns, M.D., and W. J. Kerr, M.D. Third edition. Price, \$5. Pp. XIV + 316, with 121 illustrations. Philadelphia: J. B. Lippincott Company, 1941.

In 1922 there appeared an unobtrusive little volume called "Body Mechanics in Health and Disease." It contained only 112 pages and 31 illustrations, sold for \$1.25 and was written by L. C. Thomas and J. E. Goldthwait, of Boston. It was designed primarily for directors of physical education in schools and gave common sense advice in regard to the better development of posture and correct body mechanics in children.

Apparently this booklet made no lasting impression. It soon passed into a state of innocuous desuetude, which lasted for twelve years.

In 1934 the book came to life again. It was now called "Body Mechanics in the Study and Treatment of Disease." It had grown considerably in size and was announced as the first edition of a new book rather than as the second edition of an old one. Its authors were Drs. J. E. Goldthwait, L. T. Brown, L. T. Swaim and J. G. Kuhns.

It was reviewed in a kindly manner by *The Journal of the American Medical Association* (104:1448 [April 20] 1935) and by the *American Journal of the Medical Sciences* (189:574 [April] 1935). To be sure, the authors spoke of the chronic patient and of chronic medicine—terms which *The Journal of the American Medical Association* regarded as deplorable. The book's purpose, however, was to show to its readers how modern orthopedic surgery may aid in overcoming many common disturbances of health and that to use one's body in a mechanically correct fashion is an important adjunct to well-being. The book fulfilled this purpose adequately and had a reasonable degree of success.

A new edition was printed in 1937, and now still a fresher one is obtainable. The chief differences between the latest model and the one of 1934 is that W. J. Kerr has appended a chapter on the relation of the heart and circulation to body mechanics, that the title has reverted to the one of 1922 and that the material throughout is better arranged.

From the viewpoint of bookmaking the 1941 model is excellent. While it is 35 pages larger than it was seven years ago, it weighs a few ounces less, so that it has a streamlined appearance. The paper is a little finer; the type is handsome, and the illustrations are clear and ingenious. The book continues to reveal to its readers how modern orthopedic surgery may aid in overcoming many common disturbances of health and that to use one's body in a mechanically correct fashion is an important adjunct to well-being. No doubt once again it will achieve a reasonable degree of success.

### **The Blood Bank and the Technique and Therapeutics of Transfusions.**

By R. A. Kilduffe, M.D., Director of Laboratories, Atlantic City, N. J., and M. DeBakey, M.D., Assistant Professor of Surgery, Tulane University of Louisiana. Price, \$7.50. Pp. 558, with 214 illustrations and 1 colored plate. St. Louis: C. V. Mosby Company, 1942.

This book represents a timely effort which must have been accomplished under great pressure. More than twenty-eight hundred articles are referred to in the bibliography, which gives an idea of the huge literature that required analysis in order to put together a satisfactory monograph on the many problems of blood transfusion.

The subject matter of the volume is well organized. A chapter on the history of transfusion precedes fifteen pertinent chapters on this general topic, including

how to build a satisfactory blood bank. The book ends appropriately with accounts of plasma transfusion and the preparation and preservation of wet or dry plasma and two concluding chapters on the technic of transfusion and its complications. The illustrations do much to clarify procedures which may appear complicated. The literary style employed is easy to follow. Everything about the volume is done handsomely. In brief, this is a book which should be widely read. It is a fine piece of work.

The only fault to be found with it is that nowadays the blood transfusion and blood bank business is so booming that new methods and viewpoints concerning it are being developed with astonishing rapidity. Fresh ideas crop up constantly, and a technic usable today is obsolete tomorrow. This particular book brings one down to July 1941 and already is several months out of date. The authors, no doubt, have met this objection and have a second edition under way through which to add the latest ideas on transfusion and blood collection in these perilous times when the proper use of blood or blood substitutes can save so many lives.

**Die Ursachen der Entstehung des Kropfes.** By J. U. Duerst, M.D., Professor of Hygiene, Faculty of Veterinary Medicine, University of Berne, Switzerland. Price, 24 francs. Pp. 539, with 82 illustrations. Berne: Medizinischer Verlag Hans Huber, 1941.

The author has succeeded in assembling a compendium of information about goiter, which commences with a detailed study of the comparative anatomy of the thyroid gland and ends with suggestions as to how various forms of goiter may be prevented. Obviously, it is the work of a careful student who is much interested in his subject.

Certain of the chapters appear of theoretic rather than practical interest. On the other hand, the volume does not pretend to be an ordinary textbook but rather is a general discussion of the thyroid from such varied points of view as how this gland is influenced by such factors as hibernation, climate, food, other endocrine glands and inheritance.

The book is well printed and illustrated. An excellent bibliography at the end includes most of the recent literature on the thyroid and the thymus. It is a good book for reference.

**Electrocardiography.** By Louis N. Katz. Price, \$10. Pp. 580, with 402 engravings. Philadelphia: Lea & Febiger, 1941.

A large number of books on electrocardiography of varying excellence have appeared during the past few years. The present work, as one might expect from the author's qualifications as a cardiac physiologist, deals with the subject in a scholarly way and in great detail. The various features of tracings, normal and abnormal, are analyzed and discussed meticulously. Indeed, in part it makes rather heavy reading because of the very detail. The book is handsomely got up and profusely illustrated with many reproductions of electrocardiograms, apparatus, diagrams, etc. The sections on theory discuss not only the author's views but the subject in general.

**Stethoscopic Heart Records.** By G. D. Geckeler, M.D. A set of 7 phonograph records. New York: The Columbia Recording Corporation, 1941.

These phonograph records contain an assortment of normal and abnormal heart sounds. Preceding each illustration, a voice explains the sound which is to be heard and its significance. Normal heart tones, arrhythmias, reduplications and many varieties of murmurs are reproduced. Although it is possible to listen with any degree of amplification, the instructions advise that the listener insert the ear pieces of his stethoscope in his ears and reduce the volume of the spoken voice to a point where it can just be heard distinctly. Unless this is carried out, faithful reproduction cannot be assured. This feature limits the use for large classroom instruction. The records should, however, be of some value to small study groups or to small sections in physical diagnosis.

# ARCHIVES of INTERNAL MEDICINE

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## SHOCK SYNDROME PRODUCED BY FAILURE OF THE HEART

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Two clearcut types of circulatory failure have emerged from the experimental and clinical studies of the cardiovascular system. The first, congestive heart failure, is the result of the inability of the heart to pump blood because of mechanical defects or disease of the heart muscle. It is characterized clinically by dyspnea, edema, prolonged circulation time, increased venous pressure and an increase in blood volume. Congestion may be present in the pulmonary circuit and absent in the systemic circulation. The second type, circulatory collapse, or shock, is the result of a diminished venous return to the heart. It is characterized clinically by the signs of a marked decrease in cardiac output and tissue anoxia, namely, pallor, cold extremities, sweating, weak pulse, low arterial blood pressure, narrowing of the field of consciousness and a normal or decreased venous pressure. The clinical pictures of congestive failure and of shock are so different that in most cases the appearance of the patient indicates which physiologic mechanism is operative in producing the circulatory failure. When congestion dominates the picture, the heart is usually at fault. When the signs are predominantly those of a striking diminution in cardiac output, the peripheral circulation is usually at fault.

It has been recognized, however, that the signs of a marked decrease in cardiac output may occur in heart disease and that under such circumstances the clinical picture may be similar to that of shock or the clinical signs both of shock and of congestive failure may be present. The clinical picture described as characteristic of shock is seen frequently in patients with acute myocardial infarction, although it may occur in the terminal stage of any form of heart disease. It is important to know whether the ischemic state of the peripheral circulation is caused by failure of the peripheral circulation or whether the entire

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clinical picture is produced by heart failure. Fishberg, Hitzig and King<sup>1</sup> studied cases of acute myocardial infarction with the clinical syndrome of shock. Patients with acute myocardial infarction without a previous history of congestive failure usually had a normal or low venous pressure and a normal or low normal plasma volume. Patients with a history of congestive failure before the onset of the clinical picture of shock had an increased venous pressure and an increased plasma volume. The circulation time was only slightly prolonged when the clinical picture of the myocardial infarction was dominated by the phenomena of shock. These authors concluded that the clinical picture of shock in myocardial infarction was the result of a diminished venous return to the heart because of peripheral pooling of blood. Fishberg<sup>2</sup> has modified his views, and in his latest publication on the subject he stated that the clinical picture of shock in myocardial infarction is the result of a marked decrease in cardiac output from acute myocardial failure.

Harrison<sup>3</sup> grouped under the term "cardiac collapse" those patients presenting a clinical picture of weakness, faintness, diminished mental acuity, pallor, cold moist skin, feeble thready rapid pulse and diminution in blood pressure, particularly pulse pressure, occurring as a result of failure of the heart. He pointed out that this clinical picture may occur in sudden and pronounced mechanical hindrance to the heart from cardiac tamponade, in extreme tachycardia due to an ectopic rhythm and in sudden severe injury to the myocardium. He stated that, in contrast to the picture in peripheral circulatory failure, dyspnea, orthopnea and rales in the lungs may be present and sometimes the veins of the neck are distended.

This report is based on the study of patients with known heart diseases who have shown the peripheral signs and symptoms of a marked decrease in cardiac output. They may be divided into two groups: (1) those with high venous pressure and the signs and symptoms usually attributed to shock, namely, pallor, cold extremities, sweating, low pulse pressure and narrowing of the field of consciousness and (2) those with normal venous pressure and the clinical signs and symptoms of shock.

The purpose of this study is to evaluate (1) the role of the heart and (2) the role of the peripheral vascular system and of the blood volume in producing the clinical picture of shock which is seen in certain patients with congestive failure of the heart and in some patients with acute myocardial infarction.

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1. Fishberg, A. M.; Hitzig, W. M., and King, F. H.: *Circulatory Dynamics in Myocardial Infarction*, Arch. Int. Med. **54**:997-1019 (Dec.) 1934.

2. Fishberg, A. M.: *Heart Failure*, ed. 2, Philadelphia, Lea & Febiger, 1940.

3. Harrison, T. R.: *Failure of the Circulation*, Baltimore, Williams & Wilkins Company, 1939, p. 41.

## METHOD

The arterial pressure was measured with a mercury manometer. The auscultatory method was used whenever possible. If no sounds were audible, the systolic pressure was determined by palpation. The heart rate was recorded by auscultation over the precordium or by counting the femoral pulse. The venous pressure was measured by the method of Moritz and von Tabora.<sup>4</sup> The arm to tongue circulation time was measured by the injection of decholin (sodium dehydrocholate).<sup>5</sup> The plasma volume was measured by the method of Gibson and Evans.<sup>6</sup> The value for the plasma volume of a normal subject of a given height was obtained from the data of Gibson and Evans.<sup>6</sup> For determining the hematocrit reading a 1.6 per cent solution of potassium oxalate was used. The serum protein was calculated from the specific gravity of the serum by the method of Kagan.<sup>7</sup>

## OBSERVATIONS

*Patients with Definitely Increased Venous Pressure and the Peripheral Signs of a Decreased Cardiac Output.*—This combination is frequently seen in the last few days of life in patients with cardiac disease who are dying of chronic congestive failure. The patient becomes less easily aroused and finally sinks into coma. He is usually dyspneic and orthopneic while conscious, but as the stupor becomes deeper, the difficulty in breathing becomes less noticeable. Cheyne-Stokes respiration is common. The face is pale and covered with cold sweat from time to time. The extremities are cold and cyanotic. The radial pulse is palpated with difficulty, if at all. The pulse pressure is low, but the diastolic pressure may be normal or elevated. It may not be possible to determine the arterial pressure by auscultation, although it can be measured by palpation in the antecubital space. At this time the carotid and femoral pulsations are usually palpable without difficulty. The veins of the neck are distended, but the veins of the extremities are constricted and frequently barely visible.

Studies on 4 of these patients showed that the venous pressure in the external jugular or femoral vein was markedly elevated and the

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4. Moritz, F., and von Tabora, D.: Ueber eine Methode beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen, *Deutsches Arch. f. klin. Med.* **98**:475-505, 1910.

5. Tarr, L.; Oppenheimer, B. S., and Sager, R. V.: Circulation Time in Various Clinical Conditions Determined by Use of Sodium Dehydrocholate, *Am. Heart J.* **8**:766-786 (Aug.) 1933.

6. Gibson, J. G., II, and Evans, W. A., Jr.: Clinical Studies of the Blood Volume: I. Clinical Application of a Method Employing the Azo Dye "Evans Blue" and the Spectrophotometer, *J. Clin. Investigation* **16**:301-316 (May) 1937.

7. Kagan, B. M.: A Simple Method for the Estimation of Total Protein Content of Plasma and Serum: I. A Falling Drop Method for the Determination of Specific Gravity, *J. Clin. Investigation* **17**:369-372 (July) 1938.

plasma volume was larger than normal. The venous pressure ranged from 22 to 41 cm. of water. In spite of the high venous pressure and large plasma volume, the veins of the extremities were frequently barely visible, and it was difficult or impossible to bleed these subjects from the antecubital veins. The venous outflow from the arm is dependent on an adequate arterial inflow into the arm, for it is not possible to pull blood out of the great veins of the thorax by suction on the collapsible arm veins.

The following case report illustrates the typical clinical picture. The other cases did not differ essentially from this one, and as the clinical picture is familiar, they are not reported in detail.

B. G., a 62 year old man, entered the Peter Bent Brigham Hospital on June 18, 1940, complaining of dyspnea and edema. He had had hypertension and repeated attacks of congestive failure for the preceding five years.

Physical Examination: The patient was cyanotic, dyspneic and edematous. The temperature was 97 F. (rectal); the pulse rate was 62 and the respiratory rate 22 per minute. The veins of the neck were distended.

There were moist rales over both lungs posteriorly. The heart was markedly enlarged. Auricular fibrillation was present. The liver was enlarged and there was ascites. The arterial pressure was 235 systolic and 135 diastolic.

Course: The patient did not improve, and on June 20 it was noted that he was cyanotic, weak and dyspneic. The administration of oxygen and the removal of 500 cc. of blood caused no change in his condition. In the afternoon of that day he became comatose, and the respiratory rate was rapid. The jugular veins were distended. The extremities were cold and cyanotic, and the veins were collapsed. The radial pulse was weak and small. The arterial pressure could not be obtained by auscultation. It was 196 mm. of mercury by palpation. The venous pressure was 22 cm. of water. The total serum protein concentration was 7.3 Gm. per hundred cubic centimeters, and the hematocrit reading was 48.2. The plasma volume was 3,420 cc., the normal plasma volume for the patient's height being 2,300 cc. Removal of blood from the antecubital vein was unsuccessful because of the slow flow. Seven hundred cubic centimeters of blood was removed from the femoral vein. After venesection the patient's general condition remained the same except for less distention of the veins of the neck. The venous pressure fell to 15 cm. of water. The arterial pressure was 160 by palpation. He died three hours later.

Autopsy (Limited to the Thorax): The postmortem observations included cardiac hypertrophy and dilatation, myocardial fibrosis, arteriosclerosis, passive congestion of the lungs, bronchopneumonia and pulmonary edema.

*Patients with a Normal or Questionably Elevated Venous Pressure and the Peripheral Signs of a Decreased Cardiac Output.*—Six patients with acute myocardial infarction and symptoms suggestive of shock were studied. One patient recovered and 5 died. Autopsy was performed in 3 cases. In the 2 cases in which autopsy was not done the diagnosis was confirmed by changes in the electrocardiogram characteristic of acute myocardial infarction. All these patients had had angina pectoris before the acute episode that brought them to the hospital. They had had

dyspnea but no other symptoms or signs of congestive failure. They showed pallor, cold extremities, sweating, narrow pulse pressure and small, constricted veins. They were dyspneic and orthopneic when conscious and usually complained of precordial pain. As the condition progressed, they became stuporous and the respiratory difficulty was less obvious. The heart rate was rapid unless heart block was present. The rectal temperature was either normal or elevated.

Examination of the lungs consistently showed moist rales at the bases. In some cases there were rales over the entire chest. Roentgenograms of the lungs always showed pulmonary congestion and edema, and, as a rule, the roentgenologic evidence was more striking than one would have predicted from the physical examination. In addition to the usual hilar congestion, consolidation of one or more lobes, suggesting lobar pneumonia, was not uncommon. Examination of the lungs at autopsy showed only intense congestion and edema.

The radial pulse was weak or absent, but the brachial, carotid and femoral pulses were usually palpable. The arterial pressure was frequently difficult to obtain by the auscultatory method because of the narrow pulse pressure. The diastolic pressure was fairly well maintained. The heart sounds were weak and distant. The peripheral blood flow in these patients was slow, as indicated by the coldness of the extremities. The veins of the extremities appeared constricted. Venous pressure readings in the arm were unsatisfactory because of the venous constriction and the slow arterial inflow. The arterial inflow to the arm was so slow that attempts at phlebotomy, with the use of the antecubital veins, were unsuccessful. The pressure in the femoral or the external jugular vein ranged from 8 to 13 cm. of water.

The plasma volume, the hematocrit reading and the serum protein concentration were determined in each case. In 5 cases the plasma volume was slightly smaller than the predicted volume based on the patient's height. In 1 case this was normal. In all but 1 of the 6 cases the hematocrit reading and the serum protein concentration indicated some degree of hemoconcentration at the time that the circulation appeared most inadequate. The arm to tongue circulation time was measured in 3 cases, in 1 of which the patient recovered. The circulation times were twenty-four, twenty-four and forty-eight seconds, respectively. The circulation time was not measured in the other 3 cases because the patients could not cooperate well enough to indicate the end point satisfactorily.

In 2 subjects venesection of the femoral vein was performed, 625 and 500 cc. of blood, respectively, being removed. This procedure caused neither clinical improvement nor a change for the worse. One patient was placed in the Trendelenburg position, without any improvement in clinical condition or arterial pressure.

In 1 patient with cold extremities and absence of the radial pulse the temperature of the skin of the fingers was recorded. The right ulnar nerve was then infiltrated with procaine hydrochloride. The skin of the right little finger and the right ring finger became 2 C. warmer than that of the other fingers (fig. 1). This indicated that the vasomotor center controlling arteriolar tone was still functioning.

The following 6 case reports illustrate the clinical picture.

CASE 1.—J. K., a white man aged 49, was admitted to the Peter Bent Brigham Hospital on Sept. 18, 1940, complaining of severe pain in the chest of thirty hours' duration. He gave a characteristic history of angina pectoris of two years' duration. He had had no symptoms of congestive failure. In September 1939 his arterial pressure was 140 systolic and 90 diastolic.

Physical Examination: The man was dyspneic, slightly cyanotic and agitated. The temperature was 98.8 F. (oral); the pulse rate was 40 and the respiratory rate 35 per minute. The extremities were cool and moist. The body was covered with perspiration. The arterial pressure was 110 systolic and 90 diastolic. The

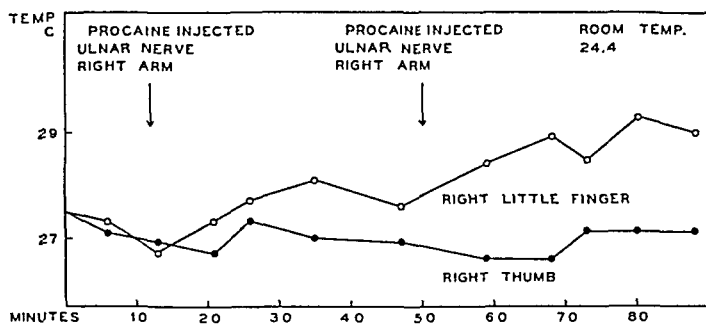


Fig. 1 (case 1).—Record of the cutaneous temperature of the right little finger and the right thumb after injection of procaine hydrochloride into the right ulnar nerve.

heart was not enlarged. There was a gallop rhythm, but no murmurs were audible. The lungs showed a few moist rales at both bases. The liver was not palpable. There was no peripheral edema. A roentgenogram of the chest showed a marked increase in the density of the upper lobe of the right lung and a moderate increase in the density of the middle and lower lobes on the same side. There was slight mottling at the base of the left lung (fig. 2A). The leukocyte count was 19,800. An electrocardiogram showed complete heart block and right bundle branch block.

Course: The patient was given a mixture of hydrochlorides of opium alkaloids (pantopon) subcutaneously and oxygen. On the day after admission Cheyne-Stokes respirations developed. During apnea he was unconscious; when hyperpneic he was restless and complained of pain over his heart. His lips were cyanotic. The face was pale, and there were beads of perspiration over the forehead. The veins of the neck were not distended. There were scattered rales over both lungs but no change in the breath sounds. A loud friction rub was audible over the precordium. The extremities and face were cold, and the body itself was cooler than normal. The skin of the trunk and extremities was extremely pale except for the hands, which had a cyanotic tint. The radial pulse was

palpated with difficulty, although the femoral and carotid pulsations were of good volume. The heart rate was 44; the temperature was 104 F. (rectal). The arterial pressure was 96 systolic and 80 diastolic. The pressure in the femoral vein was 9.5 cm. of water. The total serum protein concentration was 8.1 Gm. per hundred cubic centimeters. The plasma volume was 2,260 cc., the normal volume for the patient's height being 2,500 cc. The hematocrit reading was 53.1.

During the evening of the patient's second day in the hospital his condition was essentially unchanged. The radial pulse was not palpable. The arterial pressure was 98 systolic and 72 diastolic. The temperature was 105 F. (rectal); the venous pressure was 11 cm. of water. A roentgenogram of the chest showed a further increase in the density of the middle and lower lobes of the right lung (fig. 2 *B*). The right ulnar nerve at the region of the elbow was blocked with procaine hydrochloride. In the ulnar side of the hand and in the fourth and fifth fingers there was an increase in cutaneous temperature of 2 C. (fig. 1). Six hundred and twenty-five cubic centimeters of blood was removed from the femoral vein. The arterial pressure after venesection was 85 systolic and 65 diastolic.



Fig. 2 (case 1).—Roentgenographic appearance of the chest. *A*, Sept. 18, 1940. *B*, September 19.

The venous pressure was 7.5 cm. of water. The radial pulse became palpable, but the patient's general condition remained unchanged. He died on September 20, seven hours after venesection.

Autopsy: The heart weighed 500 Gm. The coronary arteries were markedly sclerosed. There was a myocardial infarct involving the apex of the left ventricle and the interventricular septum. The shadows in the lungs, demonstrated roentgenologically, were caused entirely by congestion and edema. There were no areas of pulmonary infarction or bronchopneumonia.

CASE 2.—L. W., a white man aged 57, was admitted to the hospital on Feb. 11, 1941, complaining of marked dyspnea of seven days' duration. He had been well until four weeks before admission, when he had a substernal sensation of choking which radiated to his back. This occurred on exertion and was relieved in a few minutes by rest. Three weeks prior to admission he was awakened from his sleep by a severe pain beneath the lower portion of the sternum, which was associated with vomiting. The pain lasted several hours. After this episode the patient had dyspnea and substernal pain on slight exertion. One week before admission he noted increasing dyspnea and experienced severe orthopnea at night.

**Physical Examination:** The patient was stuporous and markedly orthopneic. The temperature was 102 F. (rectal); the heart rate was 152, and the respiratory rate was 40 per minute. He was perspiring profusely. The skin of the face and body was extremely pale. The lips and nail beds were cyanotic. The skin of the hands had a purplish tint. The radial pulse was not palpable, and the arterial pressure could not be obtained. The femoral pulse could be felt but was weak. The veins of the neck were not distended. The heart was slightly enlarged to percussion. The heart sounds were barely audible. There was no murmur or friction rub, and the rhythm was regular. The liver could not be felt. There was slight edema of the lower portion of the legs. The leukocyte count on admission was 20,000. An electrocardiogram showed changes characteristic of an acute anterior myocardial infarction. A roentgenogram of the lungs, taken shortly after admission to the hospital, revealed marked diffuse mottling, located chiefly about the hili (fig. 3*A*). The base of the right lung was obscured. The plasma volume determined one hour after admission was 2,700

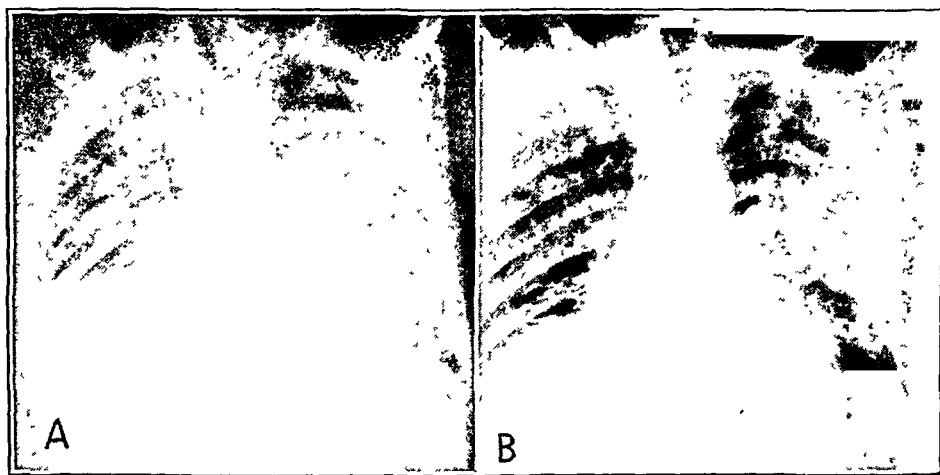


Fig. 3 (case 2).—Roentgenographic appearance of the chest. *A*, Feb. 11, 1941. *B*, February 13.

cc., the normal volume for a person of the patient's height being 3,000 cc. The hematocrit reading was 45.6, and the serum protein concentration was 7.5 Gm. per hundred cubic centimeters. The pressure in the femoral vein was 11 cm. of water. The circulation time was twenty-four seconds.

**Course:** The patient was given morphine sulfate subcutaneously, strophanthin intravenously and oxygen. He improved slightly. His dyspnea became less severe. His arterial pressure three hours after admission was 95 mm. of mercury by palpation and six hours after admission was 102 systolic and 90 diastolic. The heart rate at that time was 128 per minute. A repeat roentgenogram of the lungs made six hours after admission showed diminution of the edema in the left lung but almost complete consolidation of the middle and lower lobes of the right lung. On the day following admission he appeared fairly comfortable, although slightly orthopneic. The arterial pressure was 90 systolic and 70 diastolic. The heart rate was 80; the hematocrit reading was 37.6, and the total serum protein concentration was 6.7 Gm. per hundred cubic centimeters. On the third day in the hospital the dyspnea was increased. His heart rate rose to 150, and the temperature rose to 101 F. (rectal). The arterial pressure remained 90

systolic and 70 diastolic. A roentgenogram of the chest showed partial clearing of the lungs (fig. 3B). The hematocrit reading was 36.8, and the serum protein concentration was 6.7 Gm. per hundred cubic centimeters. On the evening of his third day of hospitalization he died suddenly.

Autopsy: The heart weighed 800 Gm. Approximately two thirds of the anterior portion of the left ventricle was completely infarcted. In the area of the infarct there was a large mural thrombus. The interventricular septum showed a few small areas of infarction. There was marked atherosclerosis of the coronary arteries, but no thrombus was found. The lungs showed pulmonary congestion and edema. There was no bronchopneumonia or pulmonary infarct.

CASE 3.—H. F., a white man aged 65, was admitted to the hospital on Feb. 2, 1941, at 1 p. m., complaining of pain in the chest and difficulty in breathing of twenty-four hours' duration. Four months before entry intermittent claudication had developed. Three weeks later he began to have attacks of nonradiating precordial pain, which were brought on by exertion and relieved by rest. Two weeks before entry he became dyspneic after climbing one to two flights of stairs. At this time he began to sleep on three pillows. The night before entry persistent substernal pain, dyspnea, insomnia and restlessness developed, which persisted until entry to the hospital.

Physical Examination: The patient was well developed and well nourished. He was propped up in bed and appeared acutely ill. The temperature was 101 F. (rectal); the pulse rate was 120, and the arterial pressure was 70 systolic and 60 diastolic. The patient was stuporous and confused but could be aroused if questioned directly. The respirations were Cheyne-Stokes in type. The face and extremities were pale. The hands and feet were warm, and the veins filled normally. The forehead was covered with perspiration. There were rales at the bases of both lungs. The radial pulse was palpable but of poor quality. The femoral pulsations were weak. The heart was enlarged to the left. The sounds were faint and distant. There was a systolic murmur at the apex and the rhythm was regular. The liver was not palpable, and there was no edema of the extremities.

Laboratory Examination: The leukocyte count was 17,800. A roentgenogram of the chest showed diffuse, streaky mottling of both lungs. The heart was enlarged. An electrocardiogram revealed changes compatible with a fairly recent posterior infarct. The blood pressure and pulse rate did not change when the patient was placed in the horizontal or moderate Trendelenburg position. The pressure in the femoral vein was 7 cm. of water. The circulation time with 10 cc. of decholin was forty-seven seconds. The plasma volume was 3,170 cc., the normal volume for a person of the patient's height being 3,000 cc. The hematocrit reading was 42.8, and the serum protein concentration was 7.3 Gm. per hundred cubic centimeters.

Course: At 9:30 p. m. on the day of admission the arterial pressure was 74 systolic and 60 diastolic; the pulse rate was 120 per minute and the temperature 101 F. (oral). The radial pulse was of good quality, and the hands were warm. The skin of the face and extremities was pale. The veins of the neck were not distended. On February 3 the patient was pale, with a cyanotic tint to his skin. The respirations were still irregular. The arterial pressure was 78 systolic and 64 diastolic and the pulse rate 120. The pressure in the femoral vein was 12 cm. of water. The hematocrit reading was 42.4, and the serum protein concentration was 7.3 Gm. per hundred cubic centimeters. A roentgenogram of the chest showed a diffuse increase in the coarse mottling of both lungs,



definitely more marked than at the previous examination. An electrocardiogram showed intraventricular block. The patient became progressively more dyspneic and died on February 4.

Autopsy: The heart weighed 450 Gm. There was infarction of the apex of the left ventricle and of the interventricular septum. The shadows in the lung, demonstrated roentgenologically, were produced by congestion and edema. There were no areas of bronchopneumonia or of pulmonary infarction.

CASE 4.—S. G., a white man aged 55, entered the hospital Oct. 3, 1940, complaining of pain of two and a half weeks' duration. He had had hypertension for ten years and had been told that his blood pressure was over 200 systolic. Left hemiparesis had developed during the past year. He had no symptoms referable to his cardiac condition until two and a half weeks prior to admission, when a sudden constricting pain developed in the upper part of the chest, which radiated to both arms and was associated with dyspnea. The pain lasted one-half hour. He had three similar attacks of pain before admission and was complaining of pain at the time he entered the hospital.

Physical Examination: The patient was slightly dyspneic. The temperature was 101 F. (rectal); the pulse rate was 120 and the respiratory rate 25 per minute. The arterial pressure was 135 systolic and 105 diastolic. The veins of the neck were not distended. The heart was enlarged, with an apical gallop rhythm and a slight systolic murmur. The rhythm was regular. The lungs were clear. The liver was not palpable and there was no edema. Signs of left hemiparesis were present. The extremities were warm, and the radial pulse was of good quality. The leukocyte count was 17,000. An electrocardiogram showed changes characteristic of an acute anterior myocardial infarct. A roentgenogram of the chest made on October 4 showed slight clouding of the left costophrenic angle and marked cardiac enlargement.

Course: Shortly after the patient's admission the arterial pressure rose to 180 systolic and 140 diastolic and he became less dyspneic. On October 7 he again complained of substernal pain. On October 8 he appeared comfortable and was able to lie flat without pronounced dyspnea. His hands were warm and the radial pulse was of good quality, but the face was pale. A moderate number of moist rales were present at the base of the right lung. There was no cyanosis or edema. The arterial pressure was 130 systolic and 108 diastolic. The venous pressure was 9 cm. of water. The serum protein concentration was 6.4 Gm. per hundred cubic centimeters. The hematocrit reading was 44. The plasma volume was 3,000 cc., which is normal for a person of the patient's height.

On October 11 the patient complained of severe dyspnea. He was weak but attempted to respond to questions. The skin was pale, and the hands and feet were cold. The upper extremities were covered with cold perspiration. The radial pulse was weak and thready, but the femoral pulse was strong. The arterial pressure could not be obtained by auscultation; it was 130 mm. of mercury by palpation. The heart rate was 120 per minute. There were fine moist rales over the lower halves of both lungs. There was no peripheral edema. The liver was not palpable. The rectal temperature was 100 F. The pressure in the left femoral vein was 8 cm. of water. The serum protein concentration was 7.2 Gm. per hundred cubic centimeters. The plasma volume was 2,770 cc. The hematocrit reading was 46.3. A roentgenogram of the chest showed pulmonary congestion and edema, particularly in the middle thirds of the lungs. There was evidence of some fluid in the lower portion of both pleural cavities.

After several hours the patient became less dyspneic and his extremities became warm. The arterial pressure could be obtained by auscultation and was 120 systolic and 105 diastolic. During the next day he had two similar attacks. He remained weak and dyspneic but had no further evidence of an inadequate peripheral circulation until October 16. At that time he became more dyspneic, his extremities became cold and he died suddenly. An autopsy was not performed.

CASE 5.—P. A., a white man aged 50, entered the hospital on Nov. 30, 1940, complaining of substernal pain of seven hours' duration. The patient had had angina pectoris for eight years. Two weeks prior to admission he began to have frequent nocturnal attacks of substernal pain. Seven hours before admission he began to have constant substernal pain, which was associated with vomiting and excessive perspiration.

Physical Examination: The patient was pale, sweating and mildly dyspneic. He was drowsy but could be roused to answer questions. The lips were cyanotic. The extremities were cold and slightly cyanotic. The radial pulse could not be felt, and the arterial pressure could not be obtained. The femoral pulse was palpable but weak. The veins of the neck were slightly distended when the patient was in the sitting position, but the veins of his hands were collapsed. The heart sounds were distant. No murmur or friction rub was heard, and the rhythm was regular. There were numerous large bubbling rales over the lower halves of both lungs posteriorly. The liver was not felt. There was no peripheral edema. The temperature was 98.8 F. (rectal); the heart rate was 120 and the respiratory rate 30 per minute. The leukocyte count was 16,300. An electrocardiogram showed changes characteristic of an acute myocardial infarction. A roentgenogram of the chest taken shortly after admission revealed coarse mottling about the hili of both lungs, extending into the bases. The plasma volume was 2,160 cc., the normal volume for a person of the patient's height being 2,500 cc. The hematocrit reading was 58.2, and the serum protein concentration was 7.4 Gm. per hundred cubic centimeters. The pressure in the external jugular vein was 13 cm. of water.

Course: The patient was given pantopon subcutaneously and oxygen, but he failed to improve. He continued to be stuporous, with rapid deep respirations, and the radial pulse was not palpable. Four hours after admission, 500 cc. of blood was removed from the femoral vein. After this there was no change in the patient's clinical condition. After phlebotomy the venous pressure fell to 4 cm. of water. Four and a half hours after admission he was given 0.5 mg. of strophanthin intravenously. There was no essential change in his condition, and he died eight hours after admission. Autopsy was not performed.

CASE 6.—T. Y., a white man aged 74, was admitted to the hospital on Jan. 24, 1941, complaining of epigastric pain and dyspnea of four hours' duration. The patient had had hypertension for three years, with an arterial pressure of 170 systolic and 110 diastolic. He gave a characteristic history of angina pectoris of one year's duration. He had had mild dyspnea on exertion during this period. Four hours before admission he experienced a sense of distress and fulness in the upper part of the abdomen, accompanied by perspiration and dyspnea.

Physical Examination: The patient was apprehensive, restless and severely dyspneic and was perspiring profusely. The temperature was 101 F. (rectal); the pulse rate was 120 and the respiratory rate 35 per minute. The arterial pressure was 110 systolic and 80 diastolic. The leukocyte count was 19,200, and the electrocardiogram showed changes characteristic of an acute anterior myocardial infarction.

Course: The patient was given morphine sulfate subcutaneously and oxygen. Venous tourniquets were applied to the extremities. He responded to therapy, and the dyspnea improved. Six hours after admission the radial pulse became feeble and the arterial pressure, determined by palpation, fell to 70 mm. of mercury. The patient was drowsy and moderately dyspneic. He appeared pale. There was moderate sweating over the forehead, arms and hands. The hands were cool. The heart sounds were faint. Many moist rales could still be heard over the posterior portion of both lungs. The pulse rate was 88 per minute, and the temperature (rectal) was 99.4 F. The venous pressure at that time was 9 cm. of water in the femoral vein. The circulation time was twenty-four seconds. The plasma volume was 2,600 cc., the normal value for a person of the patient's height being 3,000 cc. The hematocrit reading was 51.8, and the serum protein concentration was 7.5 Gm. per hundred cubic centimeters. A roentgenogram of the chest taken at this time showed congestion at the base of the right lung, obscuring the costophrenic angle. The heart was slightly enlarged. The patient improved gradually. Eight hours after admission his arterial pressure was 88 systolic and 60 diastolic; eighteen hours after admission it was 94 systolic and 70 diastolic. The following day the patient was still slightly orthopneic, but his arterial pressure had risen to 110 systolic and 70 diastolic. His radial pulse was of good quality. The hematocrit reading at that time was 46.1, and the serum protein concentration was 6.5 Gm. per hundred cubic centimeters. He continued to improve, and the dyspnea and the rales in his lungs disappeared. The plasma volume, measured again on January 27, was 2,600 cc., with a hematocrit reading of 48.8. The venous pressure at this time was 3 cm. of water in the antecubital vein, and the circulation time was nineteen seconds. He was discharged home improved.

#### COMMENT

The patients studied showed clinical evidence of a marked decrease in cardiac output. The heart sounds were weak and distant, even in those patients with normal auriculoventricular conduction. The pulsations in arteries the size of the radial and brachial vessels were feeble and in some cases absent. The femoral and carotid pulses were palpable but of diminished amplitude. The peripheral blood flow was markedly diminished, as shown by the coldness and pallor of the skin and by the difficulty in obtaining blood from the antecubital veins. The narrow pulse pressure in the presence of a fairly normal diastolic pressure suggested that the cardiac output also was diminished. This was particularly significant as evidence of a decrease in cardiac output in cases 1 and 6, in which the heart rates were 44 and 88, respectively. The relatively normal diastolic pressure indicated that the arteriolar constriction was generalized and that the blood flow in the visceral organs was also slow.

The clinical picture in hemorrhage and traumatic shock resembles in many ways the clinical picture described here. In hemorrhage and traumatic shock many of the signs and symptoms are known to be produced by the marked decrease in cardiac output, resulting from a diminished blood volume and a diminished venous return to the heart. The question arises as to whether the physiologic basis of the decrease in cardiac output in the patients described here is the same as in patients

with traumatic shock and hemorrhage. In the patients studied here the decrease in cardiac output could be caused by failure of the heart to maintain a normal blood flow in the presence of an adequate venous return, or it could result from a diminished venous return to the heart due to a markedly diminished blood volume or to pooling of blood in dilated peripheral veins or capillaries. In the patients with chronic congestive failure and an increased venous pressure it is apparent that the venous return to the heart is normal. The blood volume is increased, and there is no evidence of hemoconcentration. The venous tone must be normal, for it is sufficient to maintain the venous pressure at a high level. The clinical picture described must therefore be due to inability of the heart to maintain an adequate cardiac output in spite of an elevated venous pressure.

In the patients with acute myocardial infarction and an inadequate peripheral circulation, the systemic venous pressure was either normal or only questionably elevated. All the patients studied showed evidence of pulmonary congestion and edema in the roentgenogram. This was confirmed at autopsy in 3 cases. It appears likely that this is the result of failure of the left ventricle of the heart, with a resultant imbalance between the right and the left ventricle and an increase in pulmonary venous pressure. In myocardial infarction the area of necrosis involves predominantly the musculature of the left ventricle and usually leaves the musculature of the right ventricle relatively intact.<sup>8</sup> It is known that other lesions of the heart which place a strain on the left ventricle are frequently associated with the sudden development of pulmonary congestion and edema<sup>9</sup> and that the systemic venous pressure under such circumstances may be normal. It is unlikely that these pulmonary changes are the result of the diminution of blood flow, since the pulmonary congestion and edema may precede the development of the shock picture or may occur in the presence of relatively normal peripheral circulation. If it is true that the pulmonary changes are the result of increased pulmonary venous pressure, then the venous return to the left side of the heart must be adequate and the clinical picture of an inadequate peripheral blood flow must result from the failure of the left ventricle to maintain an adequate cardiac output. Further evidence that peripheral pooling of blood and an inadequate venous return were not producing the clinical picture was obtained by venesection in 2 cases. The removal of 500 and 625 cc. of blood, respectively, by venesection did

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8. Levine, S. A.: Coronary Thrombosis: Its Various Clinical Features, *Medicine* 8:245-418 (Sept.) 1929.

9. (a) Weiss, S., and Robb, G. P.: Cardiac Asthma (Paroxysmal Cardiac Dyspnea) and Syndrome of Left Ventricular Failure, *J. A. M. A.* 100:1841-1846 (June 10) 1933. (b) Fishberg.<sup>2</sup>

not aggravate the clinical picture, as it would have done if the fall in cardiac output were the result of a decreased venous return to the heart.

The plasma volume tended to be somewhat decreased, and there was evidence of hemoconcentration in the patients with acute myocardial infarction. The degree of increase varied, and it was never sufficient to account for the clinical picture. The decrease in plasma volume may have resulted from leakage of fluid into the lungs.

Marked prolongation of the arm to tongue circulation time was present in only 1 of the 3 cases in which it was measured. Intense pulmonary congestion and edema were shown by roentgenologic examination in case 2, in which the circulation time was twenty-four seconds. Less marked congestion was present in case 6, in which the circulation time was also twenty-four seconds. Case 2 demonstrates that marked pulmonary congestion and edema may occur from acute heart failure without the striking prolongation of circulation time frequently seen in more chronic forms of heart failure. The fact that the circulation time is not greatly prolonged cannot be used as evidence that there is little disturbance in the pulmonary circulation. The demonstration that the blood volume is not increased in acute heart failure may partially account for the observation that prolongation of the circulation time is less striking in this condition than in chronic congestive failure of the heart.

Failure of the left ventricle from acute myocardial infarction is more often accompanied by signs of an inadequate peripheral blood flow than is failure of the left ventricle due to hypertension or disease of the aortic valve. In patients with hypertension or disease of the aortic valve, the peripheral circulation usually appears relatively normal and the cardiac output is not markedly decreased.<sup>9a</sup> This difference may be due to the fact that the musculature of the left ventricle is often extremely necrotic in cases of myocardial infarction and hence is unable to follow Starling's law of the heart<sup>10</sup> and maintain the cardiac output by increasing the diastolic volume of the heart. In cases of left ventricular failure from hypertension and disease of the aortic valve, the compensatory mechanism by which the cardiac output is maintained may eventually fail, and in the last few days or hours of life a fall in arterial pressure and intense peripheral vasoconstriction may dominate the clinical picture.

The cases of acute myocardial infarction reported here were selected for study because the patients had the signs of a marked decrease in cardiac output which persisted for hours or days and was usually fatal. In the cases of myocardial infarction in which the fall in cardiac output does not completely dominate the picture, many other factors may affect the circulation. Pain may produce peripheral vasoconstriction and

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10. Starling, E. H.: *The Linacre Lecture on the Law of the Heart*, London, Longmans, Green & Company, 1918.

sweating. If the patient is anxious and apprehensive, the circulation may even appear to be more rapid than normal. In many patients with acute myocardial infarction, pulmonary edema may develop and yet the peripheral circulation may not appear inadequate. Other patients with myocardial infarction will show slow heart rates from vagal inhibition. Still others will have a fall in arterial pressure without any evidence of peripheral vasoconstriction. Certain patients will have postural fainting or other types of syncope. When complications, such as pulmonary or mesenteric emboli, occur, the clinical picture may be altered and signs of a decreased cardiac output may occur without pulmonary congestion.

This study shows that when patients with chronic congestive failure or myocardial infarction present the clinical picture considered characteristic of shock, the heart rather than the peripheral circulation is primarily at fault. We feel that the term shock should not be applied to the signs of a decreased cardiac output due to heart failure. It should be restricted to those conditions in which the cardiac output is diminished because of a decreased venous return and not because of myocardial weakness.

#### SUMMARY

A clinical picture which is similar in certain respects to that observed in surgical shock or hemorrhage is sometimes seen in patients with chronic congestive failure or with acute myocardial infarction. The patients present signs of a decreased peripheral blood flow with diminished or no radial pulse, cold extremities, narrowed pulse pressure and a relatively well maintained diastolic pressure.

The patients with a previous history of congestive failure had an elevated systemic venous pressure. The patients with acute myocardial infarction without previous congestive failure had a normal systemic venous pressure but exhibited marked pulmonary congestion and edema.

There was evidence of slight hemoconcentration in the patients with acute myocardial infarction. This may be due to loss of fluid into the lungs.

Because of the simultaneous presence of evidence of diminished peripheral blood flow and evidence of congestion either of the pulmonary or of the systemic venous bed, it is thought that the clinical picture is produced by failure of the heart, rather than by an inadequate venous return due to a decrease in blood volume or to peripheral pooling of blood.

The terms peripheral circulatory failure and shock should not be applied to the signs of a decreased cardiac output due to heart failure. They should be restricted to those conditions in which the cardiac output is diminished because of an inadequate venous return.

This work was done with the technical assistance of Rosamond Piotti, S.B.

# SEVERE FORMS OF CHICKENPOX IN ADULTS

WITH AUTOPSY OBSERVATIONS IN A CASE WITH ASSOCIATED  
PNEUMONIA AND ENCEPHALITIS

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In 1873 Trousseau <sup>1</sup> wrote in his famous work on clinical medicine: "No physician has ever seen a patient die of chickenpox, though, of course, there may be a fatal issue from some complication independent of the exanthematous fever." Today the benign nature of chickenpox and its infrequency in adults are emphasized in all textbooks of medicine. McKinley (1935) <sup>2</sup> stated: "The disease is never fatal." Serious complications are rare and usually the result of secondary infection of the specific lesions with pyogenic organisms, especially streptococci. Bullowa and Wishik (1935) <sup>3</sup> found a mortality rate of 0.4 per cent and complications in 5.2 per cent of 2,534 cases of chickenpox recorded at the Willard Parker Hospital during a five year period, Jan. 1, 1929, to Dec. 31, 1933. The most common complications were otitis media, abscess, pneumonia, lymphadenitis, cellulitis, septicemia and erysipelas. Among the 2,534 cases were 21 instances of pneumonia, 5 of encephalitis and 3 of nephritis. These authors gave the comparative incidence of pneumonia among cases of the common contagious diseases as follows:

	Chickenpox	Scarlet Fever	Diphtheria	Measles	Pertussis
Total no. of Cases	2,534	5,433	2,758	5,962	1,189
Incidence of pneumonia, %	0.8	1.5	4.1	12.0	19.0

Empyema was more common after pneumonia in cases of chickenpox (14 per cent) than after pneumonia in cases of any of the other

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1. Trousseau, A.: *Clinical Medicine: Lectures Delivered at the Hotel-Dieu, Paris*, translated from the third revised and enlarged edition by J. R. Cormack and P. V. Bazire, Philadelphia, P. Blakiston, 1882, vol. 1, p. 136.

2. McKinley, E. B., cited by Gay, F. P.: *Agents of Disease and Host Resistance*, Springfield, Ill., Charles C. Thomas, Publisher, 1935, p. 1220.

3. Bullowa, J. G. M., and Wishik, S. M.: *Complications of Varicella*, *Am. J. Dis. Child.* **49**:923-932 (April) 1935.

contagious diseases except scarlet fever (36 per cent). The causative organism in the pneumonia associated with chickenpox was almost always a streptococcus and most frequently *Streptococcus haemolyticus*. Details of the 8 cases of death in this series at the Willard Parker Hospital have been furnished us in a personal communication by the pathologist, Dr. Vera B. Dolgopol. Of the 8 patients, 1 was 30 years of age; all the others were children under 6½ years of age. In all cases slight to severe lobular pneumonia was evident at postmortem examination. In some of the cases of septic infection bacteria were present in blood vessels or in alveoli. The exudate consisted of polymorphonuclears and some macrophages. "In no case was the pneumonia of a peribronchial type, which is considered characteristic of virus pneumonias."

Among 775 patients with chickenpox, admitted to the Cincinnati General Hospital between 1913 and 1926, 19.4 per cent of whom were over 20 years of age, Mitchell and Fletcher<sup>4</sup> found only 1 instance of complicating nephritis and 4 instances of complicating bronchopneumonia. They reported only 2 deaths in the series: One child died of streptococcic meningitis following furunculosis; another contracted chickenpox while suffering from fatal tuberculous bronchopneumonia.

Shuman<sup>5</sup> found that less than 10 per cent of 2,200 patients with chickenpox admitted to the Willard Parker Hospital from January 1935 to July 1938 were over 20 years of age. In a personal communication he stated: "We had several cases of pneumonia among our adult patients with chickenpox, but this was incidental. We lost none of these patients."

Among 29,250 cases of chickenpox recorded in Vienna, Austria, from 1894 to 1899, inclusive, von Genser (1903)<sup>6</sup> found the patients in 522 cases, or 1.78 per cent, were over 14 years of age and only 70 were over 30 years of age. In this connection, it is of some interest that during the past twelve months at the Colorado General Hospital we have had 5 patients with chickenpox only 1 of whom was a child; the other 4 were adults, all over 26 years of age.

In the older age groups pneumonia or encephalitis arising in the course of this disease has never been described pathologically. In 1936 an unusual and severe epidemic<sup>7</sup> of chickenpox was reported

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4. Mitchell, A. G., and Fletcher, E. G.: Studies on Varicella, *J. A. M. A.* **89**:279-280 (July 23) 1927.

5. Shuman, H. H.: Varicella in the Newborn, *Am. J. Dis. Child.* **58**: 564-570 (Sept.) 1939.

6. von Genser, T.: Sind Varizellen eine ausschliessliche Kinderkrankheit? *Wien. med. Wchnschr.* **53**:124-127 (Jan. 17) 1903.

7. Millous: Une épidémie de varicelle maligne au Cameroun, *Bull. Acad. de méd., Paris* **115**:840-843 (June 16) 1936.



among the natives in French Cameroun, with 370 deaths among 1,919 patients. The majority of those affected were adults. Unfortunately, no pathologic studies were included in the report.

It is our purpose to report 2 cases of severe chickenpox complicated by pneumonia and, in addition in the fatal case, by encephalitis and nephrosis. Both patients were healthy, robust men, who had contracted the disease from children, in whom it ran the usual mild course.

#### REPORT OF TWO CASES

*CASE 1.—E. B., male, 40 years old; chickenpox, acute bronchopneumonia; bloody sputum, coma and marked nitrogen retention; death; complete postmortem examination.*

This man entered Colorado General Hospital Dec. 31, 1940 in a stuporous condition and therefore was unable to give a coherent history of his illness. From his landlord it was learned that the 7 year old son of the patient had come down with chickenpox on December 9. Father and son had slept in the same bed every night thereafter until the father's admission to the Colorado General Hospital. It is possible that the severity of E. B.'s illness might have been due to this intimate and continuing exposure to the chickenpox virus. He was taken sick on December 27, and his rash was rapidly developing on December 28. On admission his body was covered with innumerable macules, vesicles, pustules and brownish crusts, typical of chickenpox. He was cyanotic, dyspneic, coughing frequently and having difficulty in getting rid of tenacious, bloody, purulent sputum. His mouth was foul; his tongue was heavily coated, and the oral and pharyngeal mucous membranes showed numerous discrete ulcerations. The eruption was heaviest over the scalp, face, chest and trunk and least over the extremities.

The pupils were equal and reacted to light; the neck was not rigid, and the knee jerks were active. The ears were normal. The abdomen was soft. The lungs were normally resonant except at the bases behind. Many moist rales were heard over the lower portions of both lungs, front and back. His temperature was 100.6 F., pulse rate 100 beats per minute and respirations 26 per minute and labored. The diagnosis of his condition was chickenpox, bronchopneumonia and dehydration.

*Treatment.*—He was placed in an oxygen tent and given 1,000 cc. of Ringer's solution in a 10 per cent solution of dextrose intravenously and  $\frac{1}{6}$  grain (0.01 Gm.) of morphine sulfate hypodermically for his extreme restlessness. The administration of 15 grains (0.97 Gm.) of sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) every four hours was started the following morning.

*Laboratory Reports.*—Sputum: Repeated smears and cultures were negative for pneumococci; no acid-fast organisms were found. A mouse was inoculated, and a type XVIII pneumococcus was reported on Jan. 3, 1941.

Urinalysis: The specific gravity of the urine was 1.024; albumin (1 plus) and pus cells (1 plus) were present.

Blood Chemistry: On January 2 the blood per hundred cubic centimeters contained 94 mg. of sugar, 92 mg. of nonprotein nitrogen, 70 mg. of urea nitrogen, and 7.2 mg. of creatinine.

Blood: The hemoglobin content was 16.1 Gm. per hundred cubic centimeters.

The blood count disclosed 4,280,000 red cells and 15,250 white cells per cubic millimeter, with 73 per cent polymorphonuclear leukocytes, 19 per cent lymphocytes, 7 per cent endotheliocytes and 1 per cent eosinophils.

*Roentgen Examination of the Chest.*—A roentgenogram (fig. 1) made at the bedside was not satisfactory on account of the patient's inability to cooperate. It showed widespread mottling throughout both lungs, most conspicuous at the bases. The heart was not enlarged. The roentgenographic diagnosis was acute bronchopneumonia involving both lungs.

*Clinical Course.*—In spite of measures directed to correct dehydration and to support his strength, the patient became progressively weaker, with lengthening periods of profound stupor and delirium. The rectal temperature varied from 100.6 to 102.6 F., the respiratory rate from 26 to 32 per minute and the pulse rate from 100 to 140 beats per minute. His condition continued to grow worse, and he died at 12:55 a. m. on January 4. A detailed report of the postmortem examination will follow the clinical history of the other case.



Fig. 1 (case 1).—A roentgenogram of the chest taken with portable apparatus at the bedside of E. B. on admission. Note widespread mottling throughout both lungs.

Just one week after the death of E. B. from chickenpox with complications, another man entered the Colorado General Hospital with severe chickenpox and pneumonia.

*CASE 2.*—A. M., male, 33 years old; chickenpox, acute bronchopneumonia; profuse bright bloody sputum, dyspnea, cyanosis, delirium, moderate nitrogen retention, pleurisy and osteomyelitis of the lower jaw; recovery.

On Dec. 24, 1940 the young daughter of this patient, a medical student, came down with mild chickenpox. Fourteen days later, on Jan. 6, 1941, the father, A. M., noted a vesicle, unmistakably a specific lesion of chickenpox, inside his mouth on the lingual aspect of the mandible over the roots of the lower left first molar tooth. This ruptured on slight pressure. Other vesicles appeared in

the mouth, and a generalized polymorphous rash typical of chickenpox rapidly developed all over his body during the following days. On the morning of January 11, he coughed up a "lot of bright red sputum." He did not feel particularly sick at this time, however, and took a soda bath for relief of itching and went back to bed. At 3 p. m. he became increasingly short of breath with alarming rapidity of the pulse and was brought into the Colorado General Hospital in a serious condition. His temperature was 104 F., pulse rate 160 beats per minute and respiratory rate 48 per minute. He was mildly delirious, very restless, dyspneic and cyanotic. He complained greatly of a sore mouth and throat. His face was purplish and puffy and was covered with vesicles, a few pustules and brownish crusts. The rash was most marked over the trunk and almost absent from the lower extremities and forearms. The pupils reacted to light and in accommodation. The neck was not rigid. The mouth showed many ulcers on the hard and soft palates and one deep ulcer on the lingual aspect of the mandible on the left side. The ears and nose were normal. Respiratory excursions were shallow, and breathing was accompanied by an expiratory grunt. The sputum was almost pure blood and was raised in drachm quantities every few minutes.

Resonance was diminished over both sides of the chest, front and back, especially at the base of the left lung. The breath sounds showed patchy areas of tubular breathing and many moist rales all over the chest, front and back on both sides.

The heart was normal in size, shape and position, and there were no murmurs. The sounds were ticktack in quality; the rhythm was regular but the rate very fast. Nothing abnormal was noted in the abdomen, genitalia or extremities.

*Roentgen Examination.*—The roentgenogram of the chest (fig. 2) made at the bedside on admission, January 11, showed innumerable small shadows throughout both lungs. The heart appeared slightly enlarged to the right. The roentgenographic diagnosis was acute widespread bronchopneumonia. The clinical diagnosis included chickenpox and acute bronchopneumonia.

*Laboratory Report.*—Sputum: The sputum was bright bloody. Typing for pneumococci was unsatisfactory. Many gram-positive cocci in pairs and short chains were evident, but no acid-fast organisms were found. Mouse inoculation was negative for pneumococci. Culture of sputum on January 12 showed numerous colonies of a hemolytic streptococcus, later identified as *Streptococcus anginosus*. Culture of the sputum on January 23, during convalescence, still showed the same organism.

Urinalysis: The specific gravity of the urine was 1.023. A trace of albumin and pus cells (1 plus) were present.

Blood Chemistry: On January 13 the blood per hundred cubic centimeters contained 80 mg. of sugar, 52 mg. of nonprotein nitrogen, 30 mg. of urea nitrogen and 2.2 mg. of creatinine. On January 14 the content of nonprotein nitrogen was 38 mg.

Blood: The content of hemoglobin was 14.6 Gm. per hundred cubic centimeters. The blood count revealed 5,600,000 red cells and 8,800 white cells per cubic millimeter, with 84 per cent polymorphonuclear leukocytes, 12 per cent lymphocytes, 3 per cent endotheliocytes, 1 per cent basophils and an absence of eosinophils. A culture of the blood was negative for growth. The Wassermann reaction was negative.

Electrocardiogram: An electrocardiogram disclosed sinus tachycardia, upright T waves in leads I and II, an inverted T wave in lead III, a PR interval of 0.14 second and a QS interval of 0.08 second.

The patient was placed at once in an oxygen tent. He was given 12 cc. of a tincture of digitalis (digifortis) intramuscularly in the first forty-eight hours and 0.5 grain (0.03 Gm.) of powdered digitalis leaves orally daily thereafter for a week. He was given 30 grains (1.94 Gm.) of sulfathiazole orally at once and 15 grains (0.97 Gm.) every four hours thereafter until the report of a culture of the sputum, made on January 12, showed a pure culture of streptococci without pneumococci. The drug was then changed to sulfanilamide.

Sixteen hours after the patient was admitted, 100 cc. of "convalescent streptococcus serum" was given intravenously, and this dose was repeated twenty-seven hours later. According to his own statement, his "extremely sore" throat was "completely relieved" after the first injection of serum.



Fig. 2 (case 2).—A roentgenogram of the chest taken with portable apparatus at the bedside of A. M. on admission. Note widespread mottling throughout both lungs. Compare with figure 1.

*Clinical Course.*—During the first two days of hospitalization the patient was extremely restless, even mildly delirious at times. He complained much of shortness of breath and pain over the base of the right lung in front on inspiration. By the end of the third day he was greatly improved. Meanwhile, on January 13, a suitable donor, who had recovered from chickenpox just four weeks previously, was found, and preparations were made for transfusion of blood. However, the transfusion was not given because of the patient's obvious improvement.

Gradually the frequency of cough and the quantity of expectoration declined. The sputum changed from bright bloody to purulent with streaks of blood but remained rusty or blood streaked for fifteen days, that is until January 26.

The graphic chart (fig. 3) shows that the patient's temperature had reached normal by the fourth day of hospitalization, or the eighth day of his illness. On the tenth day in the hospital acute pleurisy developed on the right side, with shortness of breath, slight elevations of temperature and pulse, much pain at the base of the right lung anteriorly and in the midaxillary line and a typical pleuritic friction rub. No effusion developed; the temperature returned to normal, and the local signs disappeared in the following four days.

Roentgenograms of his chest were made at the bedside on the first, seventh, twelfth and sixteenth days of hospitalization and several times after he left the hospital. The one (fig. 2) made on admission showed the same widespread mottling, interpreted as small patches of bronchopneumonia, reported

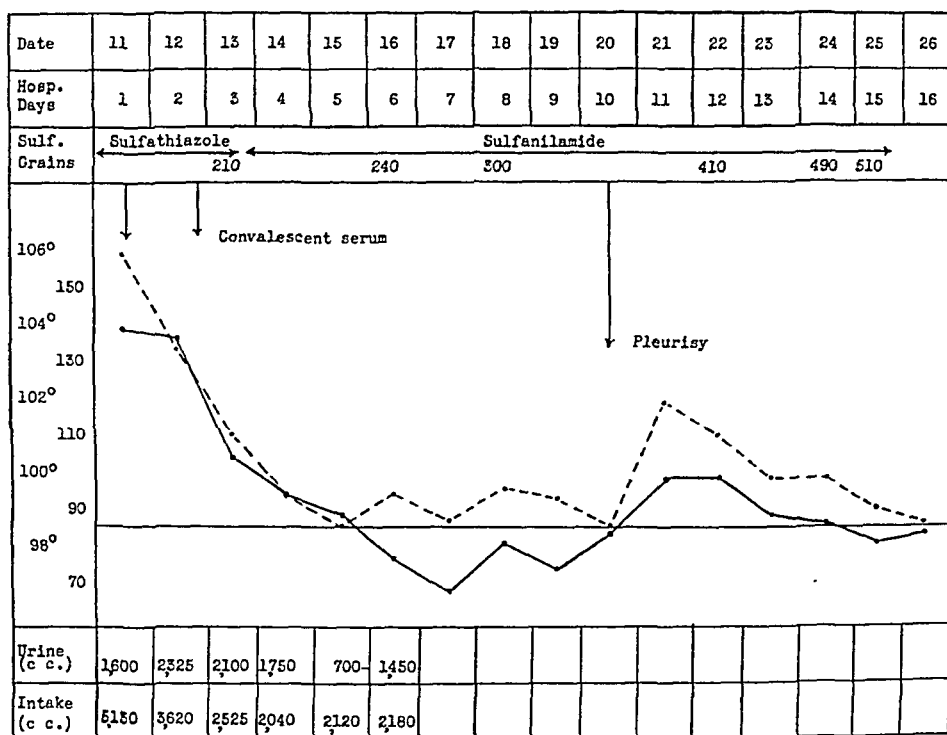


Fig. 3 (case 2).—The temperature chart of A. M., a 33 year old man with varicella and associated pneumonia followed by recovery, January 1941. The solid line represents the temperature, and the broken one signifies the pulse rate, both recorded daily at 4 p. m. Note the points at which convalescent serum was given intravenously.

for E. B., the preceding patient. The areas of bronchopneumonia decreased steadily in number and definition but were still evident as pea-sized or smaller areas of density, especially in the midzone of the left lung, on the patient's discharge from the hospital. A stereoscopic roentgenogram (fig. 4) made on June 1 at a distance of 6 feet (183 cm.) showed complete clearing.

As mentioned previously, the first specific lesion noted was a vesicle on the inside of the mouth. This vesicle became secondarily infected and remained sore until February 13, fifteen days after the patient left the hospital. At that time a small piece of alveolar process was extruded, and the ulcer thereon promptly

healed, leaving a small scar. A. M., a graduate dentist, agreed with his medical attendants that this was not a coincident abscess of the tooth but, apparently, a small area of osteomyelitis associated with the infected vesicle. A roentgenogram of the jaw made on June 1 showed complete healing.

At present (July 14), five and one-half months after leaving the hospital, A. M. is in good condition. He bears the scars of his widespread eruption but has no complaints except a slightly rapid pulse and some unusual shortness of breath on moderate exertion.

The death of E. B. from chickenpox just one week before the admission of A. M. with a remarkably similar clinical picture and the striking resemblance of the roentgenograms of the chests of the two men put the resident and attending staffs much on the alert.

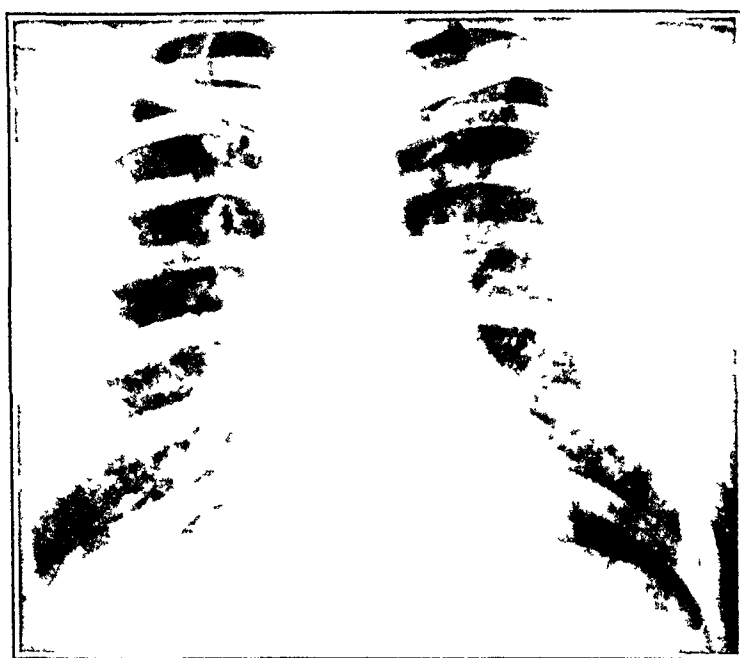


Fig. 4 (case 2).—A roentgenogram of the chest taken from a distance of 6 ft. (183 cm.) with the patient in the anteroposterior position. Note that the clearing is almost complete except on the left side in the midzone.

It was thought that A. M. had bronchopneumonia due to (1) the virus of chickenpox; (2) the combined effects of the virus of chickenpox and a secondary invader, such as a streptococcus, a pneumococcus or a staphylococcus, or (3) a streptococcus, a pneumococcus or a staphylococcus without the participation of the virus of chickenpox. It was also thought that the profuse, bright bloody sputum indicated extreme pulmonary congestion, the result in some measure of a failing heart, as well as of acute inflammation of the lung.

Doubtless the prompt use of digitalis and oxygen was helpful, but we were definitely of the opinion that "convalescent streptococcus serum" played an important part in A. M.'s recovery. This is not the time

or place to discuss at length the value of "convalescent serum" in the treatment of streptococcic infections. Suffice it to say that the reports of Baum<sup>8</sup> and others,<sup>9</sup> as well as our own observations at the Colorado General Hospital, indicate the usefulness of this form of serum therapy. Occasionally, the results have been strikingly beneficial after other methods of treatment, including chemotherapy, have failed. In the case of A. M., the serum was furnished by Baum and was collected by him from adults who had recovered from scarlet fever. The first 100 cc. was pooled serum and was given before cultures from the sputum of A. M. were available to test its agglutinating power. Of the second 100 cc., 50 cc. came from an adult who had had scarlet fever in July 1940. The serum collected in December 1940 showed the highest ability (4 plus) to agglutinate the streptococci isolated from the patient's sputum in almost pure culture. An additional 50 cc. of serum came from another adult who had had scarlet fever in May 1940. The serum was collected in October 1940. It also showed the highest ability (4 plus) to agglutinate the streptococci isolated from A. M.'s sputum. The agglutination tests were done by Dr. Francis McConnell-Mills. The hours of intravenous serum administration are indicated on the temperature chart (fig. 3). Reference has already been made to the patient's own report of prompt relief of pain and soreness in the throat following its use. It is also worthy of note that the streptococcus in this case was identified by Miss E. K. O'Toole, of the department of bacteriology, as *Str. anginosus*, a type of streptococcus not infrequently associated with scarlet fever. The use of scarlet fever convalescent serum was, therefore, not inappropriate. It should be emphasized that chemotherapy and serotherapy were used not because of a conviction that the pneumonia was purely streptococcic in origin but because we thought the streptococcus was a secondary invader of importance in the throat, possibly in the lungs or possibly elsewhere. Since the pneumonia in the first case was adjudged to be virus in type on the basis of histologic examination to be described shortly, the conclusion seems justified that the pneumonia in the second case was of similar nature. It is doubtful whether sulfanilamide has any beneficial effect on this

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8. Baum, H. L.: A Method of Specific Treatment in Certain Streptococcic Infections, *Arch. Otolaryng.* **20**:504-512 (Oct.) 1934; Specific Treatment of Various Streptococcic Infections with Human Convalescent Serum, *Colorado Med.* **32**:876-881 (Nov.) 1935; Further Observations on the Use of Specific Immune Serums in the Treatment of Streptococcic Infections, *Ann. Otol., Rhin. & Laryng.* **45**:969-978 (Dec.) 1936.

9. Platou, E. S.; Dwan, P. F., and Hoyt, R. E.: Streptococcus Convalescent Serums (Scarlatinal), *J. A. M. A.* **116**:11-15 (Jan. 4) 1941. Lyons, C.: Immuno-transfusion and Antitoxin Therapy in Hemolytic Streptococcus Infections, *ibid.* **105**:1972-1975 (Dec. 14) 1935. Hoyne, A. L.; Levinson, S. O., and Thalhimer, W.: Convalescent Scarlet Fever Serum, *ibid.* **105**:783-789 (Sept. 7) 1935.

type of pneumonia. Stimson<sup>10</sup> recently said, "No sulfonamide compound has yet been found which has any effect on infections caused by a filterable virus."

Although the specific protective value of serum from patients convalescent from chickenpox is not established and its curative value is untested, doubtless because of the low mortality rate of the disease, nevertheless A. M.'s desperate condition on admission to the hospital demanded that preparations be made to give him whatever help there might be in the serum or blood of a patient recently recovered from chickenpox. It was fully appreciated that serum injections after a virus has penetrated susceptible cells have not proved of therapeutic value. Measles may be an exception.

On January 13, blood from such a patient was secured but not used because A. M. seemed much improved.

#### AUTOPSY OBSERVATIONS (CASE 1)

A complete autopsy was performed eight hours post mortem. An abstract of the important positive observations follows:

*Gross Examination.*—The body was that of a well developed, well nourished, middle-aged, white man, presenting externally a generalized vesicular eruption. Over the scalp and face the lesions were older and covered by dark brown crusts. They were more recent over the shoulders, chest and abdomen. The distribution was least on the distal aspects of the extremities. The vesicles were discrete and easily ruptured and liberated a clear, serous fluid. The base of a ruptured lesion was raw and slightly hyperemic. When the body cavities were opened no free fluid was found.

*Lungs:* The right lung weighed 1,125 Gm. and the left one 945 Gm. They presented similar changes. The visceral pleura was thin and transparent and displayed moderate, anthracotic mottling. The consistency of each lung on palpation was diffusely nodular, with intervening crepitant zones. On section the cut surface of the lung was purplish red and bloody, and the nodular zones were indistinct and without definite relation to the bronchi or blood vessels. The arterial branches presented moderate, patchy atherosclerosis, and the bronchi contained abundant brown and blood-stained, tenacious secretions.

*Trachea:* At several points small patches of pseudomembrane were firmly adherent to the underlying mucosa. The surface appeared red and hemorrhagic when the pseudomembrane was stripped away. The largest patch measured 0.9 cm. in diameter.

*Kidneys:* The left kidney weighed 285 Gm. and the right one 240 Gm. They were greatly enlarged but of normal shape. The capsule was thin and transparent, stripping easily in each instance to leave a smooth, purplish red surface. The cut section was diffusely congested. The cortex of the left kidney measured 0.7 cm. in thickness, and the pyramids were purplish red and well defined. A moderate amount of peripelvic fat was present, and the pelvic mucosa showed scattered petechial hemorrhages. The right kidney was essentially similar.

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10. Stimson, P. M.: Some Aspects of the Common Contagious Diseases, *Bull. New York Acad. Med.* 17:532-547 (July) 1941.



Brain: The brain weighed 1,625 Gm. The meninges were not remarkable except that the vessels of the pia-arachnoid showed mild congestion. No exudates were demonstrable. The arteries over the base displayed moderate, patchy atherosclerosis, but there was no narrowing or occlusion at any point. Numerous frontal sections were made; the cerebral white matter at all levels presented widespread petechial hemorrhages. The pons and cerebellum were similarly affected. The lateral ventricles were not dilated.

*Microscopic Examination.*—Lungs: The composite picture described here is based on sections treated with the following stains: hematoxylin and eosin, the Gram-trinitrophenol stain for bacteria, Weigert's stain for elastic tissue and fibrin,

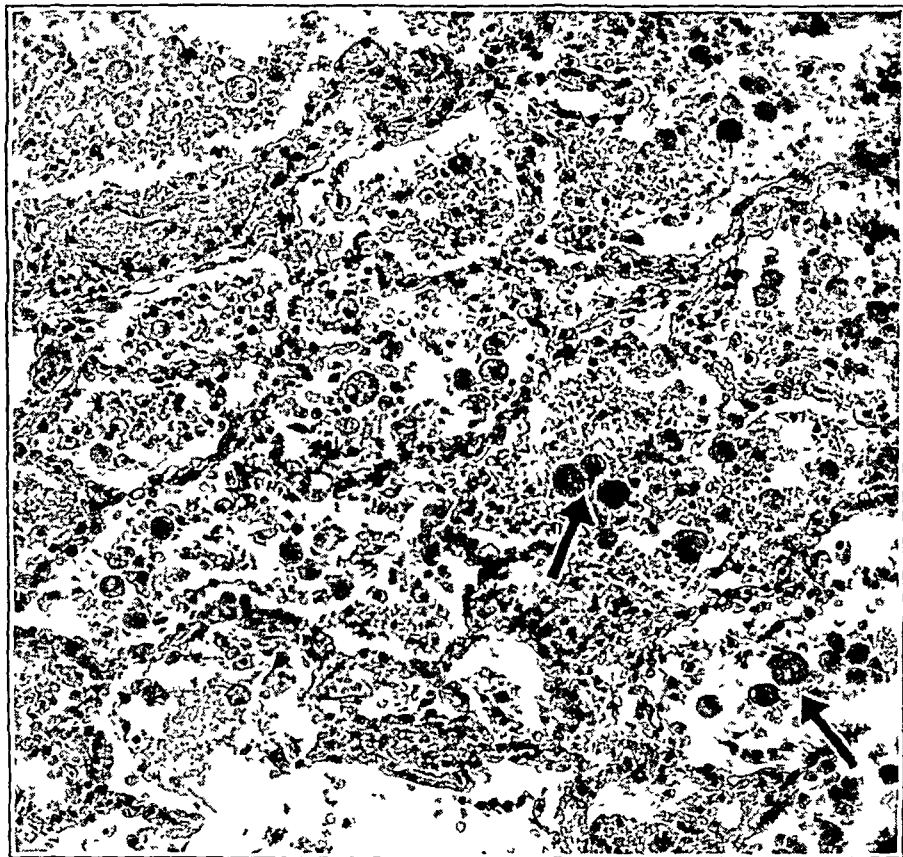


Fig. 5 (case 1).—A section of lung. Note the large mononuclear phagocytes in the exudate. Hematoxylin and eosin;  $\times 225$ .

scarlet red for fat and prussian blue for iron. The visceral pleura was composed of a thin layer of connective tissue lined at several points by prominent cuboidal mesothelium. It contained focal deposits of anthracotic pigment. In the parenchyma numerous patches of inflammation were evident, some discrete and lobular and many confluent. The alveoli therein were lined by a hyaline membrane and contained red cells and large mononuclear phagocytes. Polymorphonuclear forms were comparatively rare or absent. Marked congestion was apparent in the alveolar septums, which also contained many mononuclear cells, occasional polymorphonuclears and swollen septal cells. A lining of tall cuboidal or columnar cells was demonstrable in many alveoli, particularly in those that were partially collapsed

and free from exudate. This lining type of cell had a round, basophilic nucleus containing many chromatin particles and an eosinophilic, homogeneous cytoplasm. Mitoses were infrequent. In occasional fields continuous rows of such lining cells were desquamated. They differed from the mononuclear phagocytes in that they usually did not contain ingested pigment, and their square cuboidal, or sometimes rectangular columnar, outline was distinct from the rounded form of the phagocyte.

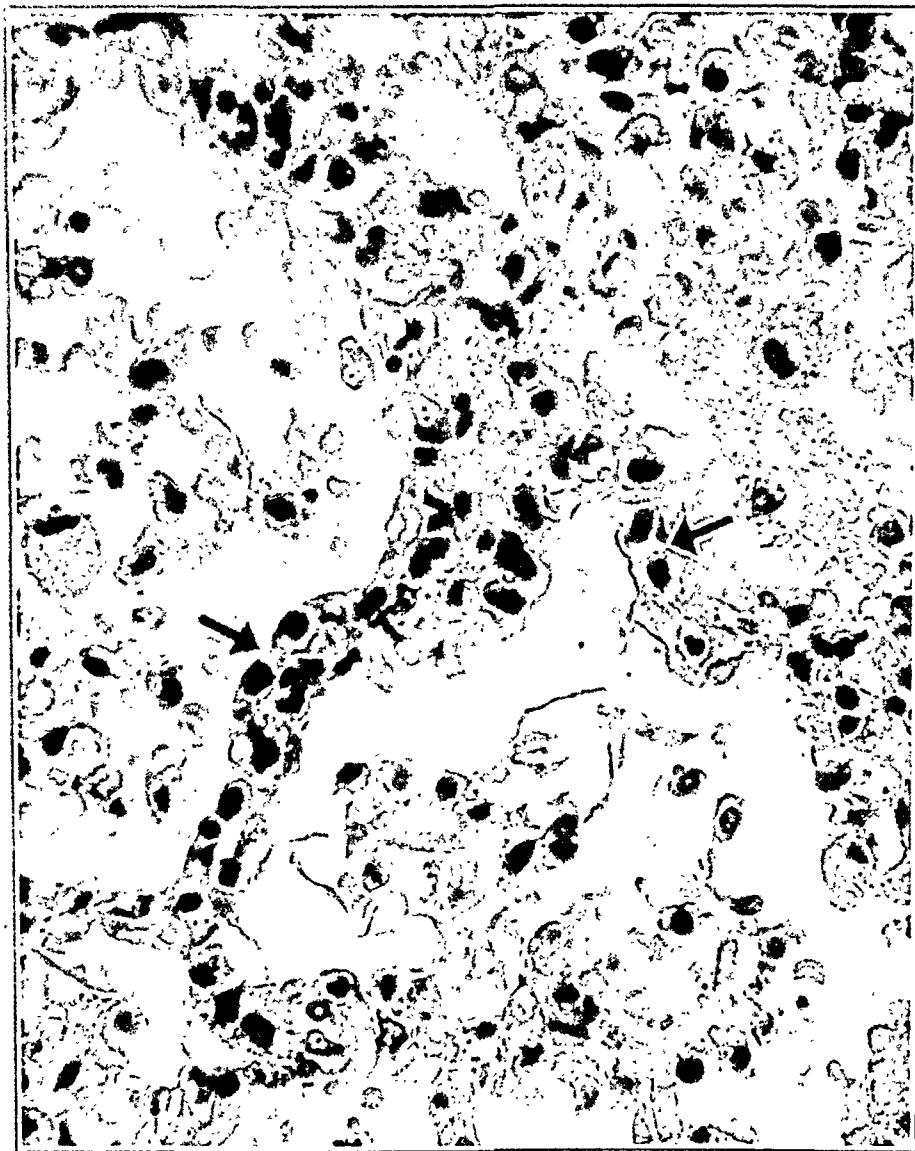


Fig. 6 (case 1).—A section of lung. Note the swelling of the septal cells in the alveolar walls, indicating the preliminary formation of the lining. Hematoxylin and eosin;  $\times 475$ .

The nucleus of the latter was smaller, darker, more homogeneous in color and more irregular in shape than that of the lining cell. In addition, there were sometimes two or three nuclei to a phagocyte, with resultant giant forms. The cytoplasm of the phagocytes usually contained brownish granules of iron and dust. Sometimes transitional forms, which did not distinctly follow either type, appeared in the process of detaching themselves from the septal walls. One obtained the impression

that both the phagocytes and the lining cells had a common origin in the septal cells. Histologic evidence was lacking that either type of cell developed from preexistent or swollen "alveolar epithelium" or as a result of downgrowth from the bronchiolar epithelium. In some groups of alveoli necrosis was most prominent, the elastic framework being swollen, split and in many cases completely dissolved. Other regions displayed only hemorrhagic foci; in a few frank fibrinous pneumonia was evident. Bacteria were rare, only an occasional gram-positive diplococcus being apparent. Several arterioles exhibited rather intense arteriolitis, with many round cells and polymorphonuclear leukocytes in the wall and surrounding adventitia. The arteriolitis appeared related to small foci of necrosis. In other arterioles

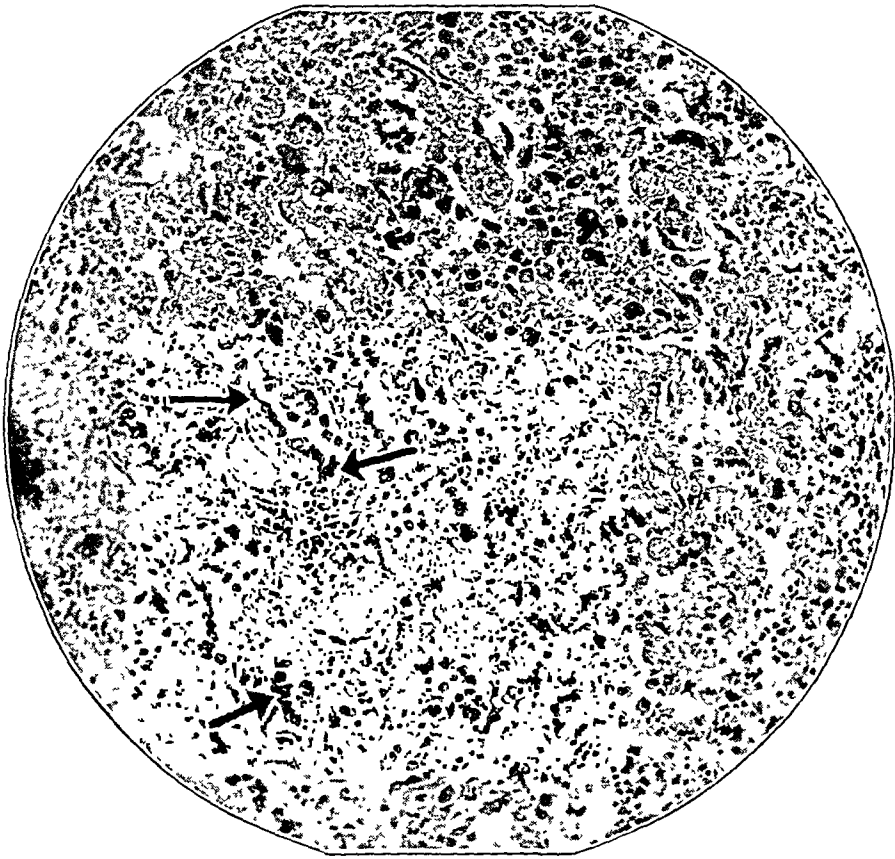


Fig. 7 (case 1).—A section of lung. Note the prominent alveolar lining desquamated in continuous rows of cells. Hematoxylin and eosin stain;  $\times 120$ .

fairly marked hyaline thickening was observed. The bronchioles and bronchi contained abundant mucinous secretion in which mononuclear phagocytes, exfoliated epithelium, polymorphonuclear leukocytes and cellular debris were prominent. The hyaline lining material in the inflammatory zones gave a basophilic, positive reaction to Weigert's stain for fibrin.

Trachea: The lining epithelium was exfoliated at several points, and in one region a membrane was attached, which was composed of a thick, fibrinous exudate in which round cells, polymorphonuclear leukocytes and cellular debris were present. The line of separation of the membrane from the underlying tunica propria was difficult to distinguish. The adjacent blood vessels were actively hyperemic,

and marked round cell and polymorphonuclear leukocyte concentrations were present thereabout. In the intact tracheal epithelium occasional intracytoplasmic and intranuclear eosinophilic inclusion bodies were apparent.

**Kidneys:** Many glomeruli were enlarged and the capillary tufts distended with red cells. The lining endothelium was swollen, and the subcapsular space occasionally contained a pink-staining, granular precipitate. The tubular epithelium showed cloudy swelling to a severe degree and in many fields hydropic degeneration in the cytoplasm. The tubule lumens also contained acid-staining, granular debris. In the cortex occasional small, wedge-shaped scars containing hyalinized glomeruli, shriveled tubules and fibroblasts, with a few round cells infiltrated throughout, could be distinguished. The medium-sized and smaller arteries exhibited slight intimal thickening and hyalinization.

**Skin:** Unilocular and multilocular vesicles were demonstrable in the epidermis. They affected mainly the upper portion of that layer except that a few larger

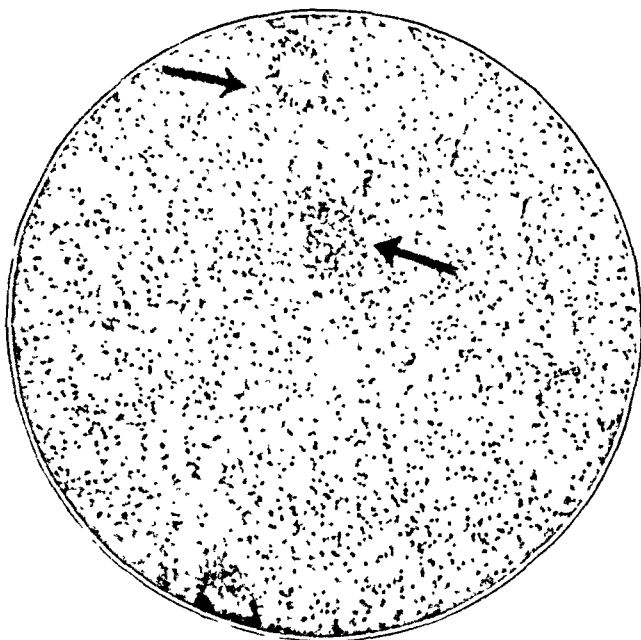


Fig. 8 (case 1).—A section of the white matter of the brain. The formation of glia nodules is evident. Nissl stain;  $\times 15$ .

lesions involved portions of the basal layers also. Infiltration of round cells and polymorphonuclear leukocytes was observed in the derma adjoining the larger vesicles. In the latter, ballooned and degenerating epithelial cells, round cells, polymorphonuclear leukocytes and occasional multinucleate giant cells with indistinct outlines were observed. The background was made up of eosinophilic cellular debris. Oil immersion examination for inclusions failed to reveal any typical acid-staining structures in the cytoplasm or nuclei of the affected epithelial cells.

**Brain:** Sections of the brain were examined by the following staining methods: Nissl, hematoxylin and eosin, Loyez, von Braunmühl, Holzer and stains for fat and elastic fibers. In the Nissl-stained sections the nerve cells in the cortex showed slight to moderate swelling in some instances and fatty degeneration in others. The majority of the nerve cells were well preserved. In other instances swelling of the satellite cells was demonstrated, and in the cortex occasional swollen microglia cells were distinguished. There was a generalized swelling of marked degree of

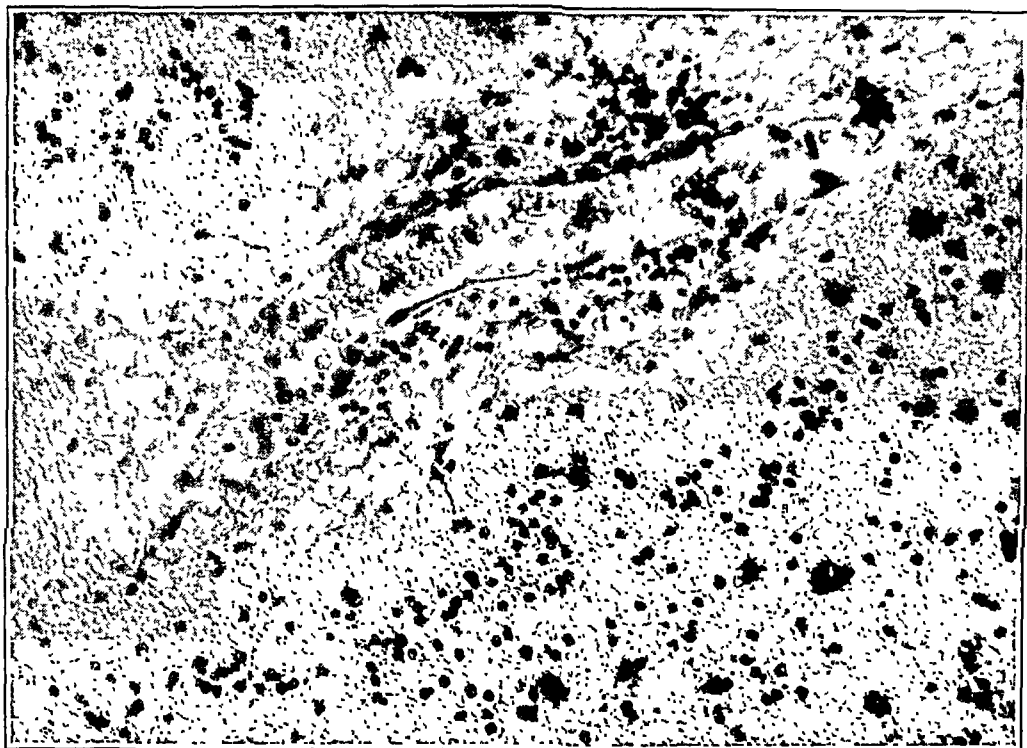


Fig. 9 (case 1).—A section of a long vein in the white matter of the brain. Note the perivascular edema and the round cell infiltration. Hematoxylin and eosin;  $\times 225$ .



Fig. 10 (case 1).—A section of the white matter of the brain. Note the focus of early demyelination. Loyez stain;  $\times 125$ .

the endothelial cells of the capillaries, both in the cortex and in the white matter. Besides petechial hemorrhages the white matter exhibited ring hemorrhages accompanied by varying combinations of central necrosis, with and without glia proliferation. Where the glial change was present, it frequently took the form of radial proliferation of microglia. Finally, in some areas of brain hemorrhage the vessel was still discernible in the center, exhibiting more or less marked necrosis of its wall. In other parts of the white matter, glia nodules or stars were present, composed of microglia and oligodendroglial cells. Some of the long veins in the white matter exhibited slight round cell cuffing, which might or might not be associated with the presence of a few pigmented, iron-containing macrophages. Others showed a prominent external sheathing by an increased number of oligodendroglia cells. Occasionally dilatation of the perivascular lymphatic spaces and some perivascular edema were noted. In places patches of fresh, mostly perivascular demyelination were observed, with only slight damage to the axis-cylinders. No proliferation of glia fibers was observed. Only a few small arterioles and venules bore traces of hyaline thickening and degeneration.

*Summary.*—The main anatomic features were as follows: (1) chickenpox, severe, generalized; (2) lobular pneumonia, severe, confluent, mononuclear, proliferative; (3) encephalitis, acute, toxic, moderate, diffuse, with purpura of the white matter, and (4) nephrosis, acute, toxic, moderate.

#### COMMENT

Before discussing the interesting findings in the lungs, brain and kidneys, we should like to examine the possibility of E. B.'s condition being atypical smallpox rather than chickenpox. The absence of a vaccination scar, the severe complications and the fatal termination suggest a more serious disease than chickenpox. However, to support our diagnosis we have, first, a history of close contact, as described. Furthermore, the character and distribution of the cutaneous lesions were typical of chickenpox, i. e., a vesicular eruption, without umbilication, appearing in crops, concentrated most heavily over the head and trunk and absent on the palms and soles. For these reasons the diagnosis of chickenpox seems correct.

*Pneumonia.*—The outstanding features of the pulmonary inflammation described in the fatal case can be summarized as follows: an exudate with predominantly large mononuclear cells; proliferation of the septal cells to form a prominent alveolar lining; alveolar necrosis and vascular damage. Bacteria were rare or absent. A survey of the literature for related forms of pneumonia in man and animals disclosed that pneumonias with a mononuclear exudate are fairly common. However, if we restrict ourselves mainly to a discussion of this type of pneumonia exhibiting proliferative features, the subdivision becomes greatly simplified.

Virus diseases are often complicated by pneumonia grossly and microscopically similar in many respects to what we have described. For example, other authors have emphasized a mononuclear, prolifera-

tive or desquamative pneumonia of distinctive type following measles, influenza and psittacosis. MacCallum<sup>11</sup> described the epidemic pneumonia occurring with measles during 1918 as of two forms, interstitial and lobular. In the former, mononuclear cells predominated, with much proliferation and desquamation of epithelium. In cases of influenza, the pneumonia is sometimes of similar character, exhibiting an interstitial distribution, proliferative features and a mononuclear exudate. Since many variations occur because of the secondary bacterial invaders, the unaltered effects of pure influenza virus are best seen in the experimental animal. We shall describe them shortly. In reporting a case of psittacosis, Güthert<sup>12</sup> described changes in the lungs somewhat similar to those in our cases. Microscopically, proliferation of alveolar lining cells was outstanding and went on to papillary projection into the lumens. The cytoplasm of the alveolar cells contained dust, pigment granules and fat droplets, the last-mentioned feature being absent in our sections. Oberndorfer<sup>13</sup> also reported a case of psittacosis pneumonia, in which he found lobar consolidation, mononuclear exudate, hemorrhage, fibrin and, in some parts, polymorphonuclear leukocytes. He summarized the changes as similar to those occurring in cases of "influenza pneumonia" and described metaplasia of the bronchiolar epithelium not unlike beginning carcinoma. In cases of rheumatic fever it is possible that a virus may be concerned, but further research is necessary before this view can be established or rejected, and we prefer not to discuss it here. We do wish, however, to refer briefly to the pathologic features of the pneumonia sometimes encountered in cases of this disease. For example, Fraser<sup>14</sup> described the pneumonia occurring in the course of acute rheumatic fever in a 20 year old woman. The striking features were proliferation of the alveolar lining cells, vascular damage, destruction of the bronchi and presence of Aschoff nodules in the interstitial tissue. The cells in the alveoli were mainly mononuclear, but in occasional regions polymorphonuclear leukocytes were predominant. In the past year we have had occasion to examine pathologic material in 3 cases which exhibited similar features and which will be reported on in a subsequent communication. In cases of pertussis many pathologists have described a fairly typical

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11. MacCallum, W. G.: *The Pathology of the Pneumonia in the United States Army Camps During the Winter of 1917-1918*, Monograph 10, Rockefeller Institute for Medical Research, 1919.

12. Güthert, H.: *Die alveolarzellige Pneumonie bei Psittakose*, Virchows Arch. f. path. Anat. **302**:707-716, 1938.

13. Oberndorfer, S.: *Pathologisch-anatomische Befunde bei Psittakosis (Papa-geienkrankheit)*, München. med. Wchnschr. **77**:311-312 (Feb. 21) 1930.

14. Fraser, A. D.: *The Aschoff Nodule in Rheumatic Pneumonia*, Lancet **1**: 70-72 (Jan. 11) 1930.

interstitial, mononuclear pneumonia with proliferative characteristics, even with formation of giant cells (Feyrter<sup>15</sup>). Goodpasture, Auerbach, Swanson and Cotter<sup>16</sup> reported cases of virus pneumonia in infants secondary to pertussis and measles. They observed, in addition to other important changes, interstitial and peribronchial pneumonitis, with polymorphonuclear and mononuclear exudate. According to their photomicrographs, proliferation was present in the alveolar walls. Inclusion bodies were observed in the epithelial cells of the respiratory tract, with secondary cellular necrosis and ulceration. Recently, Adams<sup>17</sup> reported primary virus pneumonitis occurring in a nursery epidemic and described the pathologic changes in 9 fatal cases. The lung sections showed mononuclear pneumonia but no proliferation of the alveolar lining cells.

Pneumonia caused by the Friedländer bacillus has been described<sup>18</sup> as producing a mononuclear exudate, but this description did not include proliferating features. In certain forms of tuberculous pneumonia the predominance of mononuclear cells in the exudate, together with lining cell proliferation, is well known. Beyond that, however, the resemblance ceases. Recently, Warren and Gates<sup>19</sup> have described the histologic features of radiation pneumonitis found in four species of normal animals and correlated the observations with the changes found in irradiated human lungs. They stated that the combination of anaplasia of the alveolar and bronchiolar epithelium, hyaline lining membrane in the alveoli and ruptured and reduplicated elastic framework was specific for radiation pneumonitis. They interpreted the changes in the epithelium as a response to injury. Hypertrophy of the alveolar cells was marked and approached that occurring in epidemic influenza pneumonia.

Animals exhibit pulmonary reactions to spontaneous or experimental virus infections, which also show many similarities. For example, as far back as 1903 Bosc<sup>20</sup> and Borrel<sup>21</sup> demonstrated in the lungs of

15. Feyrter, F.: Ueber die pathologische Anatomie der Lungenveränderungen beim Keuchhusten, Frankfurt. Ztschr. f. Path. **35**:213-255, 1927.

16. Goodpasture, E. W.; Auerbach, S. H.; Swanson, H. S., and Cotter, E. F.: Virus Pneumonia of Infants Secondary to Epidemic Infections, Am. J. Dis. Child. **57**:997-1011 (May) 1939.

17. Adams, J. M.: Primary Virus Pneumonitis with Cytoplasmic Inclusion Bodies, J. A. M. A. **116**:925-933 (March 8) 1941.

18. Olcott, C. T.: Friedländer Bacillus Pneumonia, Am. J. Path. **9**:959 (Nov.) 1933.

19. Warren, S., and Gates, O.: Radiation Pneumonitis, Arch. Path. **30**:440-460 (July) 1940.

20. Bosc, F. J.: Les épithéliomas parasitaires. La clavelée et l'épithélioma claveleux, Centralbl. f. Bakt. (Abt. 1) **34**:517-526, 1903.

21. Borrel, A.: Épithélioses infectieuses et épithéliomas, Ann. Inst. Pasteur **17**:81-122 (Jan.) 1903.



sheep suffering from spontaneous sheep pox proliferating mononuclear reactions in the alveoli, which they called true neoplasms. Another disease, Montana chronic progressive pneumonia,<sup>22</sup> described by Cowdry and Marsh<sup>23</sup> among others, occurs naturally in sheep and is believed to be due to a virus. This differs from sheep pox in that a definite mononuclear exudate fills the alveoli in many cases. It is characterized also by a prominent mononuclear lining in the alveoli, which creates an adenomatous appearance. Experimental virus infections are more numerous and offer the advantage that the character of the infection and the time of death can be controlled. Rivers, Berry and Sprunt<sup>24</sup> induced psittacosis pneumonia in monkeys and rabbits and studied the disease in its various stages by killing the animals at regular intervals. They found in the early periods hemorrhage, fibrin masses and peribronchial and perivascular consolidation, the exudate being composed of mononuclear cells and polymorphonuclear leukocytes. After the fourth day mononuclear cells predominated and continued to do so up to the time of clinical improvement and resolution. Cellular proliferation in the alveolar walls was also characteristic, and it was difficult to distinguish these cells from those lying free in the alveolar exudate. Straub<sup>25</sup> used a strain of influenza virus obtained from Laidlaw and evoked in mice a mononuclear interstitial pneumonia. It was characterized, in addition, by fibrinoid necrosis of the bronchiolar epithelium and in surviving animals by metaplasia of the bronchiolar epithelium and proliferation into the alveoli. Muckenfuss, McCordock and Harter<sup>26</sup> found that in the rabbit, small amounts of vaccine virus could elicit an interstitial, proliferative mononuclear reaction in the lung similar to that which has just been described.

Dochez, Mills and Mulliken<sup>27</sup> and Gordon, Freeman and Clampit<sup>28</sup> found a virus occurring naturally in certain strains of mice that did not

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22. This disease is related to jagziekte, occurring in South Africa.

23. Cowdry, E. V., and Marsh, H.: Comparative Pathology of South African Jagziekte and Montana Progressive Pneumonia of Sheep, *J. Exper. Med.* **45**:571-585 (April) 1927.

24. Rivers, T. M.; Berry, G. P., and Sprunt, D. H.: Psittacosis: I. Experimentally Induced Infections in Parrots, *J. Exper. Med.* **54**:91-104 (July) 1931.

25. Straub, M.: The Microscopical Changes in the Lungs of Mice Infected with Influenza Virus, *J. Path. & Bact.* **45**:75-78 (July) 1937.

26. Muckenfuss, R. S.; McCordock, H. A., and Harter, J. S.: A Study of Vaccine Virus Pneumonia in Rabbits, *Am. J. Path.* **8**:63-71 (Jan.) 1932.

27. Dochez, A. R.; Mills, K. C., and Mulliken, B.: A Virus Disease of Swiss Mice Transmissible by Intranasal Inoculation, *Proc. Soc. Exper. Biol. & Med.* **36**:683-686 (June) 1937.

28. Gordon, F. B.; Freeman, G., and Clampit, J. M.: A Pneumonia-Producing Filtrable Agent from Stock Mice, *Proc. Soc. Exper. Biol. & Med.* **39**:450-453 (Dec.) 1938.

appear to cause spontaneous disease, the carriers being healthy. On intratracheal injection serially of emulsified lung tissue, however, pneumonia characterized by mononuclear infiltration, hemorrhage and edema was produced. The bronchiolar epithelium was well preserved, and there was no proliferation of the alveolar lining cells. Weir and Horsfall<sup>29</sup> followed up the work on acute virus pneumonitis by inoculating throat washings from human patients intranasally into the mongoose. After serial passages they were able to produce extensive pulmonary consolidation, with the microscopic features of extensive edema filling the alveoli and causing thickening of their walls. The sparse cellular exudate was almost entirely mononuclear. The bronchial epithelium was well preserved, and perivascular or peribronchial cellular infiltration was absent. No lining cell proliferation in the alveoli was described.

A different point of view was expressed in 1935 by Sprunt, Martin and Williams,<sup>30</sup> who denied that mononuclear pneumonia is typical of the form produced by viruses. In their experiments they induced similar pulmonary changes by intratracheal injection of staphylococcus toxin and, to a lesser degree, with the toxins of streptococci and *Corynebacterium diphtheriae*. Later the same group<sup>31</sup> evoked a pulmonary inflammation in rabbits with pure cultures of Bordet-Gengou bacilli that could not be differentiated from that occurring in cases of human pertussis, influenza or psittacosis. They obtained similar results with typhoid bacilli. Shortly after World War I, Winternitz, Smith and McNamara<sup>32</sup> demonstrated pulmonary inflammation with epithelial proliferation in experimental animals in which they had introduced weak solutions of hydrochloric acid intratracheally. They stated that the reaction was similar to that which they had observed in human beings who had died of influenza or who had inhaled toxic war gases. Subsequent investigators have induced similar pulmonary changes with other chemicals, but a discussion of their experiments is beyond the scope of this paper.

In conclusion, we have drawn attention to another virus agent as a possible cause for the mononuclear and proliferative pneumonia which occurs in man, namely, the chickenpox virus. Although the literature

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29. Weir, J. M., and Horsfall, F. L., Jr.: The Recovery from Patients with Acute Pneumonitis of a Virus Causing Pneumonia in the Mongoose, *J. Exper. Med.* **72**:595-610 (Nov.) 1940.

30. Sprunt, D. H.; Martin, D. S., and Williams, J. E.: Interstitial Bronchopneumonia: I. Similarity of a Toxin Pneumonia to That Produced by the Viruses, *J. Exper. Med.* **62**:73-83 (July) 1935.

31. Sprunt, D. H.; Martin, D. S., and Williams, J. E.: Interstitial Bronchopneumonia: II. Production of Interstitial Mononuclear Pneumonia by the Bordet-Gengou Bacillus, *J. Exper. Med.* **62**:449-456 (Sept.) 1935.

32. Winternitz, M. C.; Smith, G. H., and McNamara, F. P.: Effect of Intra-bronchial Insufflation of Acid, *J. Exper. Med.* **32**:199-204 (Aug.) 1920.

contains numerous references to a virus cause for this form of pneumonia in man, its appearance in a few bacterial infections, notably whooping cough, must be admitted. In experimental animals chemicals, various toxins and certain bacteria can reproduce the pathologic changes observed in human autopsy material. It has been our experience that in the majority of human autopsy specimens exhibiting this type of pulmonary inflammation the etiologic agent is a virus.

*Encephalitis.*—Neurologic complications of varicella are not rare, and Bergman and Magnusson<sup>33</sup> mentioned 150 cases reported up to 1939, of which 114 were observed after 1925. However, the number of cases with autopsy reports sufficient for evaluation is much smaller. Underwood<sup>34</sup> gathered 6 such cases up to 1935, and Bergman and Magnusson added 4 others.<sup>35</sup> The observations reported hitherto are not quite uniform, and it is difficult to say whether a typical histologic picture of "encephalitis varicellosa" can be established. If one omits nonspecific changes, such as congestion or meningitis, possibly caused by secondary complications, in only 4 instances in the literature has involvement of the brain been exhibited which is comparable to that seen in the present case.<sup>36</sup> In the case reported by Zimmerman and Yannet,<sup>37</sup> a girl 13 months of age became feverish, irritable and restless on the third day following the appearance of an extensive chickenpox eruption. On the next day she had two generalized convulsions and died during a third, which occurred that night. There was widespread, nonspecific degeneration in the ganglion cells of the brain and cord. In

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33. Bergman, R., and Magnusson, J. H.: Studie über Enzephalitis bei Varizellen mit besonderer Berücksichtigung der Spätprognose, *Acta pædiat.* **26**:31-61, 1939.

34. Underwood, E. A.: The Neurological Complications of Varicella: A Clinical and Epidemiological Study, *Brit. J. Child. Dis.* **32**:83-107 (April); 177-196 (July); 241-263 (Oct.) 1935.

35. The fact that "varicella encephalitis" usually runs a benign course is illustrated by the case reported by Lucksch (Ueber Enzephalitis nach Varicellae, Variola, nach Vaccination und nach Morbilli, *Med. Klin.* **28**:1554-1557 [Nov. 4] 1932): A boy aged 14 months died of bronchopneumonia and purulent otitis media, seven weeks after having recovered from chickenpox. During the course of the latter disease he had had marked nervous symptoms of nearly two weeks' duration. Careful examination of the nervous system at autopsy failed to reveal damage due to the former involvement, the encephalitis associated with the chickenpox having left no trace.

36. Wohlwill reported peculiar histiocytic perivascular infiltration in the central nervous system in a case of chickenpox but was in doubt as to the etiology of this process (*Pathologisch-anatomische Beiträge zur Frage: Varicellen und Nervensystem*, in Volume jubilaire en l'honneur du Professeur G. Marinesco, Bucarest, Société Roumaine de Neurologie, Psychiatrie et Endocrinologie, 1933, pp. 683-697).

37. Zimmerman, H. M., and Yannet, H.: Nonsuppurative Encephalomyelitis Accompanying Chickenpox, *Arch. Neurol. & Psychiat.* **26**:322-332 (Aug.) 1931.

addition, diffuse, perivascular demyelination was observed in the white matter of the parietal lobes, with extensive formation of fat granule cells. A moderate number of such cells was also present in the meninges. Occasional small focal hemorrhages were found in the cortex. No perivascular inflammatory lesions were seen. The authors stressed the relation of this condition to encephalitis following measles or vaccination and also to certain forms of acute, toxic encephalitis in children, with an absence of perivascular infiltration. Van Bogaert<sup>38</sup> described the case of a 12 year old girl who died seventeen days after the onset of nervous symptoms (eighteen days after the appearance of chickenpox and twenty-seven days after having fallen ill of febrile tonsillitis). Clinically, there were symptoms of a meningeal reaction, acute ataxia, choreatic movements, pyramidal disturbances, insomnia and delirium with visual hallucinations. Histologically, degeneration of the nerve cells was observed in many areas of the gray matter and was associated with microglia reactions. Far more characteristic, however, was the condition encountered chiefly in the white matter. Numerous foci of demyelination were observed, with some involvement of the axons and with activity of gitter cells storing the disintegrated myelin. Fibrous gliosis had ensued, and a secondary inflammatory reaction in the neighboring vessels composed of lymphocytes, plasma cells and macrophages laden with fat was discernible. A mild perivascular inflammatory reaction was also present in the meninges and around certain cortical capillaries. The author expressed the belief that the condition in this case was more akin to acute multiple sclerosis than to the encephalitis following measles or vaccination. In the cases of Dagnélie and Dubois, cited by Underwood,<sup>34</sup> the patient was a girl 8 months of age who showed excessive congestion, particularly in the white matter, associated in certain areas with perivenous demyelination. There was no alteration in the axons, and no inflammatory changes could be found. Death had occurred within twenty-four hours after the onset of brain symptoms. The case reported by Bergman and Magnusson<sup>33</sup> was only briefly described histologically. After apparent recovery from chickenpox a boy aged 12 years showed symptoms of acute encephalitis, which terminated fatally in six days. The brain was swollen and congested, and round cell perivascular infiltration and focal destruction of the parenchyma were observed in the basal ganglions and medulla. Finally, the experimental studies of Eckstein<sup>39</sup> should be mentioned.

38. van Bogaert, L.: Histopathologische Studie über die Encephalitis nach Windpocken (Encephalitis postvaricellosa), *Ztschr. f. d. ges. Neurol. u. Psychiat.* **140**:201-217, 1932.

39. Eckstein, A.: Klinische und experimentelle Untersuchungen zur Frage der Varicellenencephalitis, *Ztschr. f. d. ges. Neurol. u. Psychiat.* **149**:176-190, 1933.

Monkeys inoculated intracerebrally with fluid from varicella blebs were killed after three to five weeks. They displayed thrombi, petechiae and perivascular infiltration over the entire central nervous system. Other animals, inoculated with the contents of the vesicles of herpes zoster, which is considered related to chickenpox, demonstrated foci of demyelination and softening, with partial involvement of the axis-cylinders.

One may gather from the histologic and experimental data that the chickenpox virus may cause disturbances of circulation; demyelination, particularly in the white matter; perivascular infiltration, also mainly in the white matter, and diffuse degenerative lesions. The changes in the brain may be related to multiple sclerosis and to perivenous encephalitis (postmorbillosa and postvaccinalis). In the case of E. B. all forms of the lesions mentioned were present, but some of them were only slight or moderate in intensity. The outstanding characteristic, both grossly and microscopically, was the vascular disturbance, which pointed to a pronounced vasotoxic action of the virus. Petechial and ring hemorrhages dominated the picture. This was a nonspecific reaction consistent with that which occurs in various toxic and infectious conditions or even after trauma. The observations in the present case are important, however, because a case of cerebral involvement following chickenpox in an adult with autopsy observations has never been reported before. Only a larger number of cases with autopsy reports will permit a more definite classification of encephalitis varicellosa. Since the disease usually ends with recovery, this will probably not be attained for some time. When an opportunity offers itself, special attention should be given to the perivascular (perivenous) demyelination, with or without lesions of the axis-cylinders, as described in the literature and as observed to a certain extent in the case of E. B.

The relation of chickenpox encephalopathy to perivenous encephalitis is by no means incompatible with a relation to multiple sclerosis. Putnam<sup>40</sup> stressed the possibility that perivenous encephalitis may develop into multiple sclerosis. He and his co-worker emphasized that the foci of multiple sclerosis which they had studied were generally perivenous.<sup>41</sup> The location of the foci of demyelination in chickenpox appears to support Putnam's views. The similarity between encephalitis varicellosa and multiple sclerosis was discussed by Spielmeyer<sup>42</sup> on the grounds

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40. Putnam, T. J.: Studies in Multiple Sclerosis: VII. Similarities Between Some Forms of "Encephalomyelitis" and Multiple Sclerosis, *Arch. Neurol. & Psychiat.* **35**:1289-1308 (June) 1936.

41. Putnam, T. J., and Alexander, L.: Disseminated Encephalomyelitis, *Arch. Neurol. & Psychiat.* **41**:1087-1110 (June) 1939.

42. Spielmeyer, W.: Vergleichend anatomische Betrachtungen über einige Encephaliden, insbesondere über den Typus der Impfencephalitis, *Ztschr. f. Hyg. u. Infektionskr.* **113**:170-191 (Nov.) 1931.

of the case reported by van Bogaert. Future observations of demyelination in cases of chickenpox encephalitis may facilitate understanding of the etiology and pathogenesis of multiple sclerosis.

*Renal Damage.*—In 1884 Henoch<sup>43</sup> was the first to report renal complications in chickenpox and presented at that time 4 cases of nephritis in children, with 1 death. The autopsy revealed "recent parenchymatous nephritis," but details of the microscopic examination were not given. The rarity of nephritis was emphasized by Denny and Baker,<sup>44</sup> who found only 52 cases of acute nephritis accompanying or following chickenpox in all the literature up to 1928. These authors, furthermore, stressed the possibility of a complicating streptococcic infection as a cause of the nephritis associated with chickenpox. In the case they reported<sup>44</sup> and in others<sup>45</sup> associated streptococcic intervention either appeared definite or could not be ruled out. In the fatal case here presented microscopic sections of lung and kidney tissue failed to show evidence of the action of the streptococcus. A brief recapitulation of the clinical pathologic findings follows:

Blood chemistry:	Nonprotein nitrogen	92	mg./100 cc.
	Urea nitrogen	70	mg./100 cc.
	Creatinine	7.2	mg./100 cc.
Urinalysis:	Specific gravity	1.024	
	Albumin	+	
	Pus cells	+	

The results of anatomic examination included the following data: The kidneys were diffusely congested and greatly increased in size and weight, i. e., they weighed 285 and 240 Gm. The average normal weight is 150 Gm. each (Saphir<sup>46</sup>). In the microscopic examination tubular damage and widespread vascular congestion were outstanding. The changes indicated toxic nephrosis rather than nephritis from the strict pathologic standpoint.

The possible effect of the sulfathiazole therapy cannot be dismissed, as renal damage following the use of the drug has been reported on numerous occasions in human beings and in experimental animals. An analysis of the dosage shows that our patient had received a total of 8 Gm. at the time the blood was drawn for the aforementioned chemical

43. Henoch, E.: Nephritis nach Varicellen, Berl. klin. Wchnschr. **21**:17, 1884.

44. Denny, E. R., and Baker, B. M., Jr.: Varicella Complicated by Acute Nephritis, Bull. Johns Hopkins Hosp. **44**:201-206 (March) 1929.

45. Tilley, J. B., and Warin, J. F.: A Severe Case of Chicken-Pox with Some Unusual Features, Brit. M. J. **1**:1265 (June 11) 1938.

46. Saphir, O.: Autopsy Diagnosis and Technique, New York, Paul B. Hoeber, Inc., 1937, p. 314.

analysis. Arnett,<sup>47</sup> to be sure, reported a toxic renal effect on a 72 year old woman who had received a total dose of only 14 Gm. He stopped the drug when intense lumbar pain, accompanied by the passage of bloody urine, developed. Abundant crystals could be demonstrated, furthermore, in the urine. Garvin<sup>48</sup> also observed crystals in the urine in 61 per cent of 54 patients under sulfathiazole treatment for pneumonia. In animal experiments performed on monkeys, mice and rats<sup>49</sup> hematuria and crystal collections sufficiently concentrated to cause obstruction in the renal tubules, ureters and urinary bladder have been described.

Our microscopic examinations of the kidney sections were performed with the aforementioned criteria in mind. The granular debris which we found in the tubule lumens was in no instance concentrated to the point of plugging and, furthermore, showed no crystals. On the basis of these considerations, we feel the more likely cause for the renal changes to be the virus of chickenpox.

#### SUMMARY

1. Two cases of severe chickenpox in adults with 1 fatality and the autopsy observations in the fatal case are presented.

2. The clinical course and the roentgenograms of the lungs are discussed.

3. A mononuclear, proliferative, lobular pneumonia is described and the literature on related forms in man and animals reviewed.

4. An instance of acute toxic encephalitis is described and compared with previously reported instances of chickenpox encephalitis.

5. Acute toxic nephrosis, arising as a complication of chickenpox, is described with reference to the autopsy results.

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47. Arnett, J. H.: Hematuria from Sulfathiazole Therapy in Pneumonia, *J. A. M. A.* **115**:362-363 (Aug.) 1940.

48. Garvin, C. F.: Renal Complications Due to Sulfathiazole, *J. A. M. A.* **116**:300-301 (Jan. 25) 1941.

49. Rake, G.; van Dyke, H. B.; Corwin, W. C.; McKee, C. M., and Greep, R. O.: Pathological Changes Following Prolonged Administration of Sulfathiazole and Sulfapyridine, *J. Bact.* **39**:45-46 (Jan.) 1940. van Dyke, H. B.; Greep, R. O.; Rake, G., and McKee, C. M.: Observations on the Toxicology of Sulfathiazole and Sulfapyridine, *Proc. Soc. Exper. Biol. & Med.* **42**:410-416 (Nov.) 1939. Gross, P.; Cooper, F. B., and Scott, R. E.: Urolithiasis Medicamentosa, *Urol. & Cutan. Rev.* **44**:205-209 (April) 1940.

# RESTING PERIPHERAL BLOOD FLOW IN THE HYPERTHYROID STATE

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It is well established that cardiac output,<sup>1</sup> blood volume,<sup>2</sup> pulse pressure<sup>3</sup> and pulse rate<sup>4</sup> are significantly increased in the hyperthyroid state. In view of this, a corresponding augmentation in peripheral blood flow would also be expected. This concept has recently received support from the cutaneous temperature studies of Kirklin and his associates<sup>5</sup>

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1. Davies, H. W.; Meakins, J., and Sands, J.: The Influence of Circulatory Disturbances on the Gaseous Exchange of the Blood: V. The Blood Gases and Circulation Rate in Hyperthyroidism, *Heart* **11**:299 (Dec.) 1924. Fullerton, C. W., and Harrop, G. A., Jr.: The Cardiac Output in Hyperthyroidism, *Bull. Johns Hopkins Hosp.* **46**:203 (Feb.) 1930. Liljestrand, G., and Stenström, W.: Clinical Studies on the Work of the Heart During Rest: I. Blood Flow and Blood Pressure in Exophthalmic Goitre, *Acta med. Scandinav.* **63**:99, 1925.

2. Chang, H.: Blood Volume in Hyperthyroidism, *J. Clin. Investigation* **10**:475 (Aug.) 1931. Goldbloom, A. A., and Libin, I.: Clinical Studies in Circulatory Adjustments: I. Clinical Evaluation of Studies of Circulating Blood Volume, *Arch. Int. Med.* **55**:484 (March) 1935. Gibson, J. G., II, and Harris, A. W.: Clinical Studies of the Blood Volume: V. Hyperthyroidism and Myxedema, *J. Clin. Investigation* **18**:59 (Jan.) 1939.

3. Sturgis, C. C., and Tompkins, E. H.: A Study of the Correlation of the Basal Metabolism and Pulse Rate in Patients with Hyperthyroidism, *Arch. Int. Med.* **26**:467 (Oct.) 1920.

4. Read, J. M.: Basal Pulse Rate and Pulse Pressure Changes Accompanying Variations in the Basal Metabolic Rate, *Arch. Int. Med.* **34**:553 (Oct.) 1924. Sturgis and Tompkins.<sup>3</sup>

5. Kirklin, O. L.; Plummer, W. A., and Sheard, C.: Measurements of the Skin Temperatures of the Extremities in Exophthalmic Goitre, Before and After Medical and Surgical Treatment, *Proc. Staff Meet., Mayo Clin.* **15**:774 (Dec. 4) 1940.



and from the work of Stewart and Evans,<sup>6</sup> who measured heat loss in hyperthyroid patients with a Hardy-Soderstrom radiometer.<sup>7</sup> By means of various calculations, the last-named authors expressed their data as blood flow to the skin in cubic centimeters per minute per square meter of body surface. Thus, they determined that the average blood flow was increased in the hyperthyroid state and decreased during iodine therapy and after subtotal thyroidectomy. Likewise, Kirklin and his associates<sup>5</sup> reported that the cutaneous temperature of the big toe was significantly elevated before surgical treatment of exophthalmic goiter and that it fell after operation. In respect to other blood beds, Roberts and Griffith,<sup>8</sup> using a capillary microscope, observed that most of the cutaneous capillaries of the forearm were open in hyperthyroid subjects.

In order to determine more directly the changes in peripheral circulation brought about by the hyperthyroid state, the venous occlusion plethysmographic method was employed in the present investigation. The three procedures previously cited are not applicable to such a study, since they do not measure total blood flow but reflect or indicate only changes in skin circulation. Moreover, since it has been shown that all portions of the extremities do not respond alike to various stimuli,<sup>9</sup> an opportunity was afforded, with the plethysmographic method, to determine separately the changes in the hand, the forearm and the leg.

#### METHOD

The investigation was performed on a series of 12 hyperthyroid patients, for 7 of whom readings were also obtained at various intervals after subtotal thyroidectomy. No distinction was made between the subjects with exophthalmic goiter and those with toxic adenoma of the thyroid. The rate of blood flow, in cubic centimeters per minute per hundred cubic centimeters of limb volume, was determined according to the technic previously mentioned.<sup>10</sup> The room temperature generally

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6. Stewart, H. J., and Evans, W. F.: The Peripheral Blood Flow in Hyperthyroidism, *Am. Heart J.* **20**:715 (Dec.) 1940.

7. Hardy, J. D., and Soderstrom, G. F.: An Improved Apparatus for Measuring Surface and Body Temperature, *Rev. Scient. Instruments* **8**:419 (Nov.) 1937.

8. Roberts, E., and Griffith, J. Q., Jr.: A Quantitative Study of Cutaneous Capillaries in Hyperthyroidism, *Am. Heart J.* **14**:598 (Nov.) 1937.

9. Abramson, D. I., and Ferris, E. B., Jr.: Responses of the Blood Vessels in the Resting Hand and Forearm to Various Stimuli, *Am. Heart J.* **19**:541 (May) 1940.

10. Abramson, D. I.; Zazeela, H., and Marrus, J.: Plethysmographic Studies of Peripheral Blood Flow in Man: I. Criteria for Obtaining Accurate Plethysmographic Data, *Am. Heart J.* **17**:194 (Feb.) 1939; II. Physiologic Factors Affecting Resting Blood Flow in the Extremities, *ibid.* **17**:206 (Feb.) 1939. Ferris, E. B., Jr., and Abramson, D. I.: Description of a New Plethysmograph, *ibid.* **19**:233 (Feb.) 1940.

varied between 25 and 27 C., and the bath temperature (the temperature of the water in the plethysmograph) was maintained at 32 C. Ten to twenty readings were obtained in each experiment, and from the average of these the rate of resting blood flow was calculated.

In addition to blood flow readings, data on the blood pressure, pulse rate and oxygen consumption per unit of time were obtained in each experiment. Changes in circulation time (decholin arm to tongue time) were followed in 2 patients.

## RESULTS

For purposes of comparison with normal subjects, the figures collected in other investigations were utilized.<sup>11</sup> In the control series it was found that the average blood flow in the hand at a bath temperature of 32 C. and a room temperature of 25 to 27 C. was 9.32 cc. per minute per hundred cubic centimeters of limb volume ( $\sigma=2.1$ ); in the forearm it was 1.77 cc. ( $\sigma=0.7$ ), and in the leg, 1.38 cc. ( $\sigma=0.5$ ).

*Resting Blood Flow.*—Examination of the table reveals that in every instance the figure obtained for resting blood flow in the forearm of the hyperthyroid patients was considerably greater than the average of 1.77 cc. for the control group. In some patients it was increased as much as three to four times this figure (J. L., E. M., D. O.). These findings are comparable to those of Herrick and her associates<sup>12</sup> in experimentally produced hyperthyroidism in dogs. The opportunity to correlate the effects of the administration of compound solution of iodine U. S. P. with blood flow offered itself in 2 cases. One patient (J. L.) showed a significant decrease in forearm blood flow, while in the other (L. M.) the change was not appreciable, the period of treatment with the iodine solution being shorter in the case of the latter. After subtotal thyroidectomy there was a definite decrease in forearm blood flow for each patient, with a return to a normal or even subnormal level in from eleven to sixty-three days after operation (fig. 1 A). The findings in the leg for the 3 patients examined were similar to those for the forearm, except that the changes were somewhat less in degree (fig. 1 B).

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11. Abramson, D. I.: Resting Peripheral Blood Flow in Hypertensive Subjects, *Proc. Soc. Exper. Biol. & Med.* **45**:127 (Oct.) 1940. Abramson, D. I., and Fierst, S. M.: Resting Blood Flow and Peripheral Vascular Responses in Hypertensive Subjects, *Am. Heart J.* **23**:84 (Jan.) 1942.

12. Herrick, J. F.; Essex, H. E.; Mann, F. C., and Baldes, E. J.: The Effect of Feeding Desiccated Thyroid Gland on the Flow of Blood in the Femoral Artery of the Dog, *Am. J. Physiol.* **105**:434 (Aug.) 1933.

In contrast to the constancy of the results obtained in the forearm, the response in the hand varied with the different hyperthyroid patients. The average rate of blood flow for the group as a whole was found to be

*Resting Peripheral Blood Flow*

Subject	Age, Yr.	Compound Solution of Iodine, Days Admin-istered	Relation to Operation, Days	Blood Flow *			Blood Pressure, Mm. Hg.	Pulse, Beats, per Min.	B.M.R., %	Circulation Time, Sec.
				Hand	Fore-arm	Leg				
M. B.	21		19 before	11.2	4.7		124/60	106	+57	9
			12 before		4.7		128/64	110	+51	9
			7 after	9.8	2.9		106/60	85		10
			35 after	11.4	1.0		110/68	86	-1	10
J. L.	57	3	13 before	5.1	6.8		130/88	92	+40	11
			2 before	6.4	3.9		136/88	78	+22	11.5
			10 after	10.7	3.3		142/90	77	+10	13
			63 after	8.1	1.4		138/80	80	+16	12.5
S. S.	25		27 before	13.0	3.8		132/88	134	+68	
			11 after	5.4	0.9		116/78	74	+ 2	
M. S.	27		4 before	14.5		3.1	120/64	110	+39	
			7 after	14.8		2.3	112/76	81		
			30 after	10.9		2.1	108/68	73	+ 7	
			63 after	5.2		1.6		70	+ 5	
E. M.	40	8	5 before	12.1	4.5		110/68	100	+40	
			4 after	9.1	3.3		110/68	70	+20	
			28 after	4.9	1.3		124/76	62	+ 5	
L. M.	42	1	7 before	9.8	5.8		126/70	88	+44	
			1 before	14.0	4.4		126/74	90	+29	
			8 after	13.1	3.8		128/80	88	+23	
			53 after	4.0	1.2		132/84	60	-13	
J. P.	52	4	1 before	11.5	5.3		156/82	112	+44	
			4 after	9.9	2.3		136/80	90	+15	
W. J.	41	18		10.4	4.1		166/76	100	+18	
A. E.	34			2.4	3.2		116/66	96	+23	
J. F.	68			15.0	2.9		184/106	116	+37	
D. O.	27	4		18.5	7.2	2.5	156/60	110	+50	
A. K.	24	14		12.5	2.8	3.3	152/86	91	+38	

\* All values for blood flow are expressed in cubic centimeters per minute per hundred cubic centimeters of limb volume.

only somewhat greater than that for the control series (11.6 cc. per minute per hundred cubic centimeters of limb volume, as compared with 9.3 cc.). Some of the individual readings, however, fell in, or definitely beyond, the upper range of normal figures (table). In the 2 subjects on whom the effect of treatment with the iodine solution was studied, a

decrease in flow in the hand was not observed; in fact, an increase appeared in 1 (L. M.). After thyroidectomy, in 4 patients there was a significant decrease in hand flow from a high normal to a sub-normal level in eleven to sixty-three days after operation (table, fig. 1 *B*). In 2 subjects, however, a definite effect on hand blood flow was not observed even thirty-five and sixty-eight days, respectively, after operation (table, fig. 1 *A*).

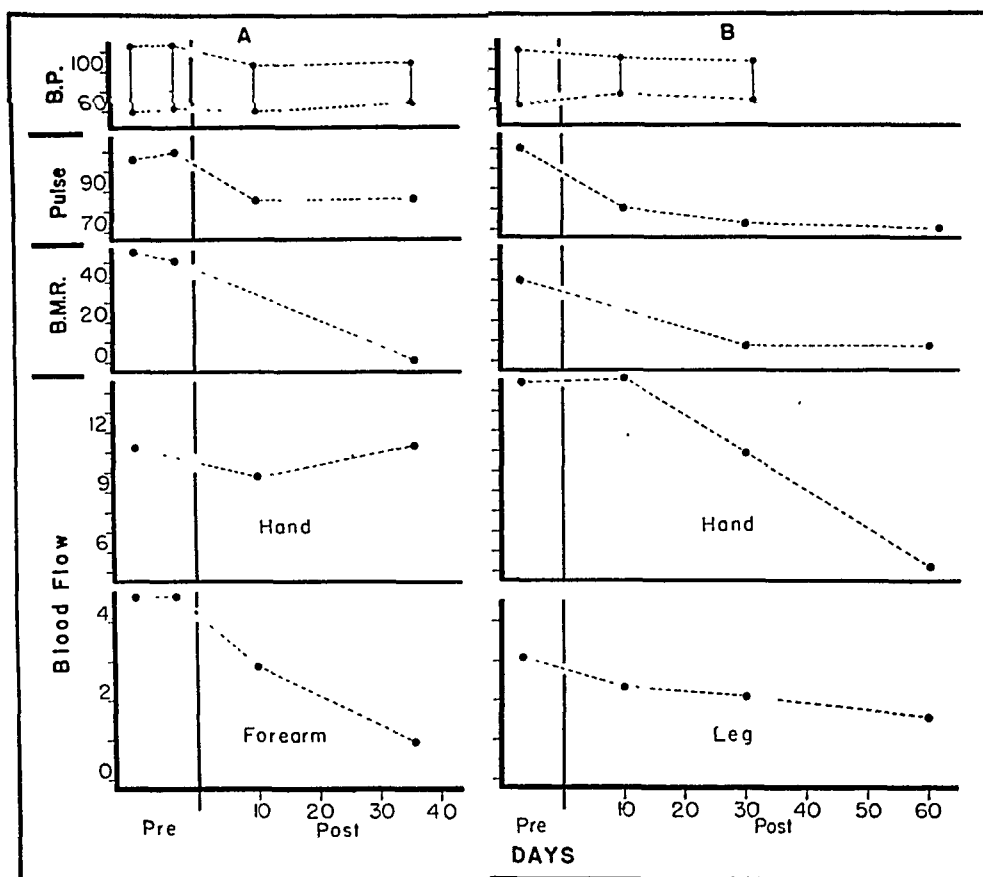


Fig. 1.—The resting blood flow (in cubic centimeters per minute per hundred cubic centimeters of limb volume) correlated with other data. *A*, subject M. B. (table). *B*, subject M. S. (table).

*Comparison of Peripheral Blood Flow Readings with Other Data.*—For the patients (M. B. and J. L.) in whom the arm to tongue circulation time was studied, there appeared to be some increase in the postoperative figures over those obtained in the hyperthyroid state. During the same period of observation a marked drop in forearm blood flow took place. With reference to the effect of thyroidectomy on pulse rate and blood pressure, it is of interest to note that the postoperative

basal levels were reached at a time when the peripheral blood flow both in the forearm and in the leg was still significantly elevated (figs. 1 and 2). Similarly, in 2 cases (patients J. L. and M. S.) the fall in oxygen consumption to within the normal range took place more rapidly than did the decrease in peripheral blood flow. Inasmuch as the changes in the hand blood flow following thyroidectomy varied in the different patients, no general correlation could be made between the blood flow in this site and the results obtained with the other procedures.

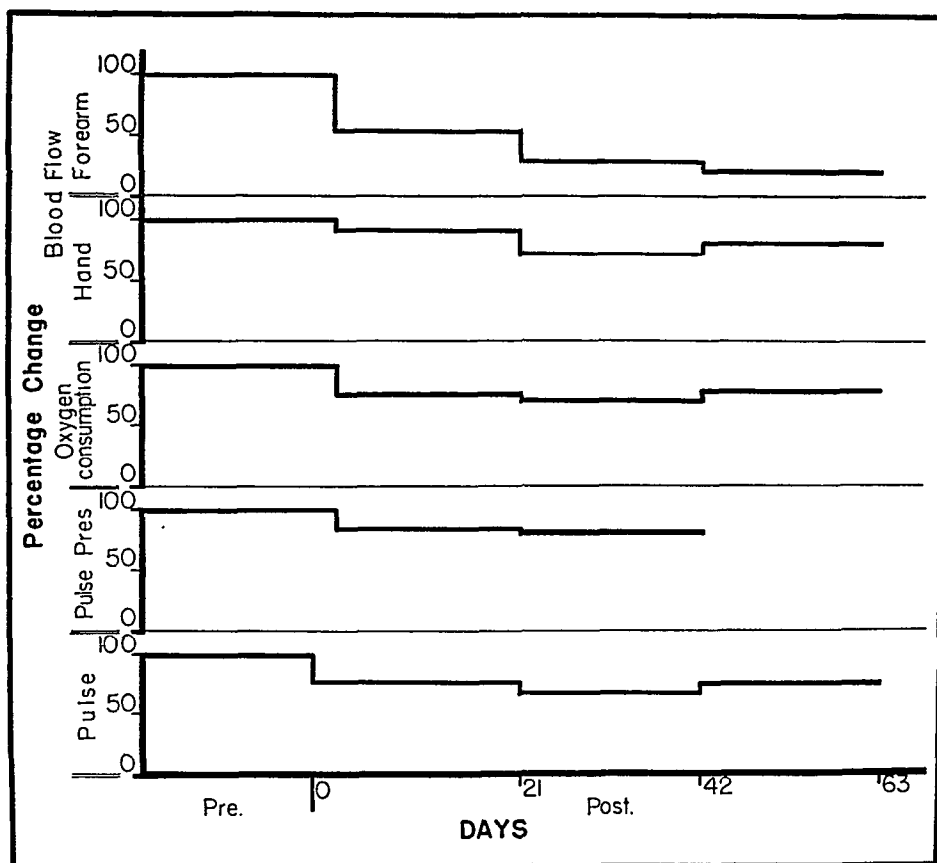


Fig. 2.—The effect of thyroidectomy. The average of data for all patients is expressed as the percentage of the highest preoperative levels. The postoperative observations are depicted in three week periods.

#### COMMENT

*Resting Blood Flow During Hyperthyroidism.*—From the preceding results it is apparent that there is a definite augmentation in the rate of resting blood flow through the forearm and leg during the hyperthyroid state. This observation is in accord with the previously known circulatory findings of an increase in cardiac output,<sup>1</sup> blood volume,<sup>2</sup> pulse pressure<sup>3</sup> and pulse rate.<sup>4</sup> The rate of blood flow in the hand, however, is not strikingly increased, since the readings for the most part

fall within the upper range of those obtained for normal subjects. In this respect, the data of Kirklin and his associates,<sup>5</sup> on the cutaneous temperature of the finger tip may be pertinent. These investigators found that only minor reductions in temperature occurred after partial thyroidectomy. Similarly, H. J. Stewart and Evans<sup>6</sup> reported that a significant change in the average cutaneous temperature of the hand did not occur after operation. G. N. Stewart,<sup>13</sup> however, using the calorimetric method, found an augmented hand flow in a single case of hyperthyroidism.

The difference between the response of the hand in the hyperthyroid state and that of the forearm and the leg may in some way be linked with the fact that the first region is composed principally of skin, with its numerous arteriovenous shunts, while in the other two regions muscle tissue predominates. Aside from this gross anatomic distinction, the nervous control of the blood vessels is also different. As has been shown recently,<sup>9</sup> the blood vessels of the hand are under the control of the vasomotor center, while those of the forearm and leg are little if at all affected by vasoconstrictor impulses. Blood flow in the hand, therefore, will be decreased by various hormonal influences and by different types of psychic and noxious stimuli. Conversely, the other two vascular beds, under similar conditions, will generally demonstrate an increase in flow, either as a result of active vasodilatation or in consequence of an augmented cardiac output.

Evidence has recently been presented which appears to indicate that the skin of the normal forearm and leg contributes little to heat dissipation under ordinary environmental conditions.<sup>14</sup> Our finding in cases of hyperthyroidism of a significant increase in total blood flow to the forearm, together with that of Roberts and Griffith<sup>8</sup> of dilated cutaneous capillaries in this site, would suggest that under such circumstances this vascular bed may play a role in heat elimination. However, it does not seem reasonable to assume that this factor alone accounts for the enhanced circulation through the forearm and the leg. Since most of the recent work favors the view that the thyroid hormone raises the catabolic activity of tissues,<sup>15</sup> it is conceivable that at least a good portion

13. Stewart, G. N.: *Studies on the Circulation in Man: The Blood Flow in the Hands and Feet in Normal and Pathological Cases*, in *Harvey Lectures, 1912-1913*, Philadelphia, J. B. Lippincott Company, 1913, vol. 8, p. 86.

14. Grant, R. T., and Pearson, R. S. B.: *The Blood Circulation in the Human Limb: Observations on the Differences Between the Proximal and Distal Parts and Remarks on the Regulation of Body Temperature*, *Clin. Sc.* **3**:119 (April) 1938.

15. Gerard, R. W., and McIntyre, M.: *The Effect of Thyroid Feeding on Tissue Respiration*, *Am. J. Physiol.* **103**:225 (Jan.) 1933. McEachern, D.: *Direct Measurements of the Oxygen Consumption of Isolated, Beating Auricles from Normal and Thyrotoxic Guinea-Pigs*, *Bull. Johns Hopkins Hosp.* **50**:287 (April) 1932.

of the augmented peripheral blood flow in hyperthyroidism is called forth by the increased oxygen demands of the muscles.

*Resting Blood Flow After Thyroidectomy.*—It is obvious from the preceding data that subtotal thyroidectomy results in a decreased rate of blood flow through the forearm and the leg, with a return to a normal level some time after operation. It is of interest that in 4 patients there was also a diminution in hand flow, from a high normal to a subnormal level. Since the length of the period during which the aforementioned changes took place was definitely greater than that in which the pulse rate and blood pressure returned to normal levels (fig. 2), the possibility suggests itself that the augmentation in peripheral blood flow in hyperthyroidism was not due solely to an increased cardiac output. If the latter were the only factor, the decrease in pulse rate and pulse pressure (these factors generally being an index of cardiac output) should have exactly paralleled the diminution in peripheral blood flow. It would appear, therefore, that the response of the peripheral blood vessels, consequent to the hyperthyroid state, is more lasting than that of the heart.

#### SUMMARY AND CONCLUSIONS

1. The rate of blood flow through the hand, forearm and leg was studied in a series of 12 hyperthyroid subjects by means of the venous occlusion plethysmographic method. In 7 of the patients opportunity was offered to observe the changes in flow for some time after thyroidectomy.

2. The average resting blood flow in the forearm and leg of the hyperthyroid subjects was significantly increased over that of a control series. After thyroidectomy there was a decrease, with a return to a normal level in eleven to sixty-three days after operation.

3. The average resting blood flow in the hand was not strikingly increased, although some of the individual readings were significantly greater than those of the control group. After thyroidectomy in the majority of cases the flow decreased to a subnormal level.

4. The rate of fall in peripheral blood flow to normal levels, subsequent to operation, occurred more slowly than did the decrease in pulse rate and pulse pressure.

Drs. J. L. Ransohoff and A. M. Wigser cooperated in the study.

# ELECTROCARDIOGRAPHIC STUDIES ON ARTIFICIALLY PRODUCED PULMONARY ARTERY OCCLUSION IN HUMAN BEINGS

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The clinical differentiation between pulmonary artery occlusion and coronary artery occlusion is difficult, and at times impossible. In the past this was a matter purely of academic interest, since treatment of both consisted of complete rest and supportive care. Now, however, when the application of specific therapy is possible, early accurate diagnosis becomes imperative. The electrocardiograph is a physical apparatus which accurately records the curves of differences in electropotential generated by the functioning heart. With any appreciable obstruction to pulmonary artery circulation (as that produced by an embolus) there is a rise in the pulmonary artery pressure gradient, and therefore increased resistance is presented to the discharge of blood from the right ventricle. On this basis, it is, *a priori*, to be suspected that there would be a disturbance in the electropotential balance which would be reflected on the electrocardiogram.

McGinn and White (1935)<sup>1</sup> coined the term *acute cor pulmonale* to designate this condition and described what they believed to be a characteristic electrocardiographic pattern, namely, (1) a prominent S wave and lowered take-off of the RS-T segment in lead I, (2) a staircase ascent of the RS-T segment in lead II and (3) a deep Q wave and an inverted T wave in lead III. All this was postulated on dilatation and partial failure of the chambers on the right side of the heart. After this report several others appeared. Barnes<sup>2</sup> attempted to differentiate the electrocardiographic contours produced by pulmonary embolus from those produced by posterior coronary occlusion. Love, Brugler and Winslow<sup>3</sup> reported their observations on 12 patients,

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From the Ross V. Patterson Heart Station, Jefferson Hospital.

1. McGinn, S., and White, P. D.: *Acute Cor Pulmonale Resulting from Pulmonary Embolism: Its Clinical Recognition*, J. A. M. A. **104**:1473 (April 27) 1935.

2. Barnes, A. R.: *Proc. Staff Meet., Mayo Clin.* **11**:11, 1936; *Pulmonary Embolism*, J. A. M. A. **109**:1347 (Oct. 23) 1937.

3. Love, W. S., Jr.; Brugler, G. W., and Winslow, N.: *Ann. Int. Med.* **11**:2109, 1938.



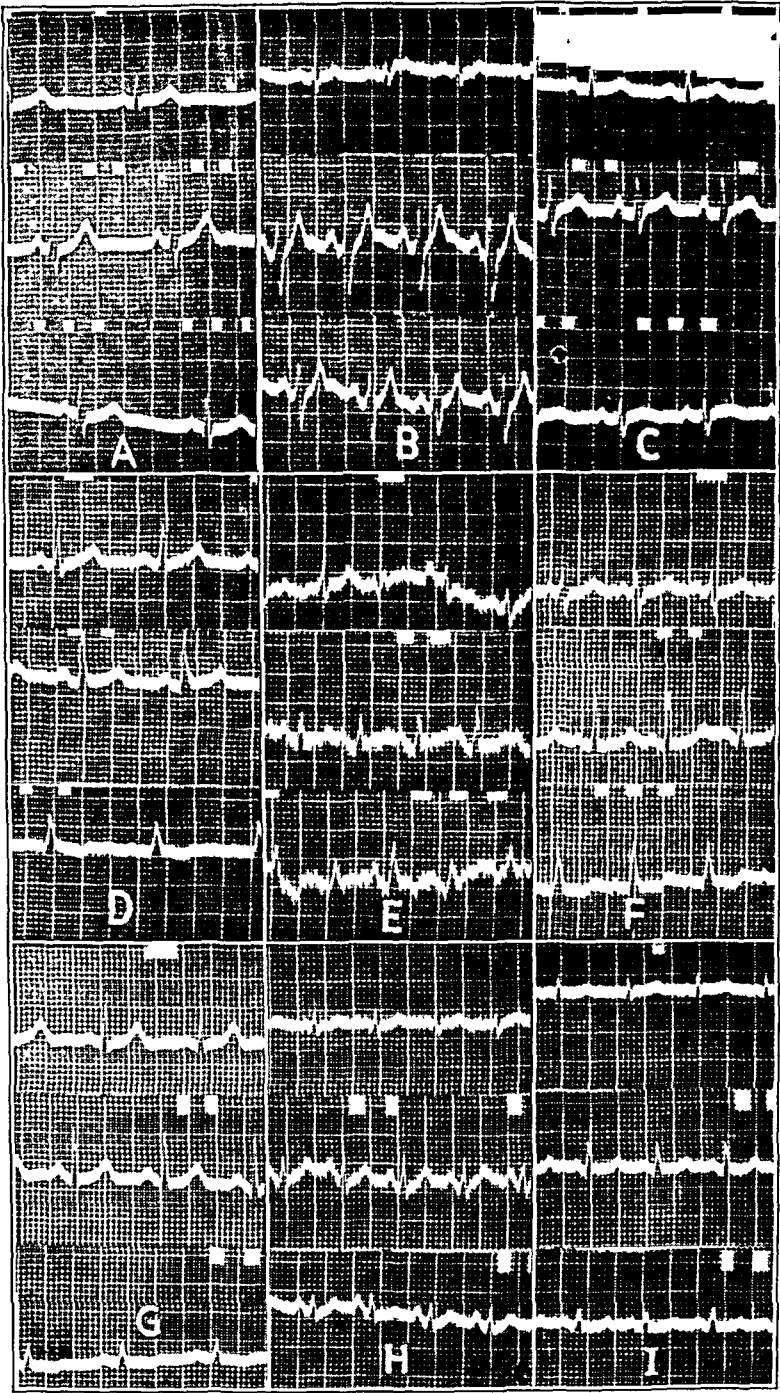


Figure 1

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7 (58 per cent) of whom showed significant electrocardiographic change, namely, depression of the RS-T segments in leads I and III, flattening and rarely inversion of the T wave in lead II and an inverted T wave in lead III, with or without a Q wave. Abnormal T waves in lead IV were noted for 5 (42 per cent) of the patients. The authors expressed the belief that from 50 to 85 per cent of the pulmonary circulation must be occluded to produce electrocardiograms with significant systemic changes. Krumbhaar<sup>4</sup> observed the changes of bundle branch block following experimental pulmonary artery ligation. It was clearly evident that pulmonary embolus produced electrocardiographic change, that electrocardiographic changes are but reflections of cardiac change, and attempts were made to explain the mechanism. Mosler<sup>5</sup> and Buchbinder and Katz<sup>6</sup> suggested that a circulatory deficiency of the coronary arteries resulted from the obstruction to blood flow. Scherf and Schönbrunner<sup>7</sup> expressed the opinion that a vagal reflex was responsible for a reduction in coronary flow. The same end was accomplished by the fall in aortic pressure, according to Haggart and Walker.<sup>8</sup> Love and Brugler<sup>9</sup> tried to take all factors into account. They pictured a cycle—the mechanical pulmonary obstruc-

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4. Krumbhaar, E. B.: *Am. J. M. Sc.* **187**:792, 1934.

5. Mosler, E.: *Med. Klin.* **43**:1555, 1931.

6. Buchbinder, W. C., and Katz, L. W.: *Am. J. M. Sc.* **187**:785, 1934.

7. Scherf, D., and Schönbrunner, E.: *Ztschr. f. klin. Med.* **128**:455, 1935; *Klin. Wchnschr.* **16**:340, 1937.

8. Haggart, G. E., and Walker, A. M.: *Physiology of Pulmonary Embolism as Disclosed by Quantitative Occlusion of the Pulmonary Artery*, *Arch. Surg.* **6**:764 (May) 1923.

9. Love, W. S., Jr., and Brugler, G. W.: *South. M. J.* **30**:371, 1937.

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#### EXPLANATION OF FIGURE 1

Case 1. *A*, preoperative electrocardiogram, with a normal axis. *B*, post-operative electrocardiogram, with a tendency to a right axis deviation and a staircase ascent of the ST segments in leads I and II. *C*, electrocardiogram made twenty-four hours after operation, with a normal preoperative contour.

Case 2. *D*, preoperative electrocardiogram, with a normal axis. *E*, post-operative electrocardiogram, with a prominent S wave in lead I, a tendency to a right axis deviation, a staircase ascent of the ST segment in lead I and an inverted T wave in lead III. *F*, electrocardiogram made twenty-four hours after operation, with a prominent S wave in lead I and a return of the axis to normal.

Case 3. *G*, preoperative electrocardiogram, with a normal contour. *H*, post-operative electrocardiogram, with a prominent S wave in lead I, a normal axis, a staircase ascent of the ST segment in lead II and low voltage throughout the entire tracing. *I*, electrocardiogram made twenty-four hours after operation, with a normal axis and low voltage throughout.

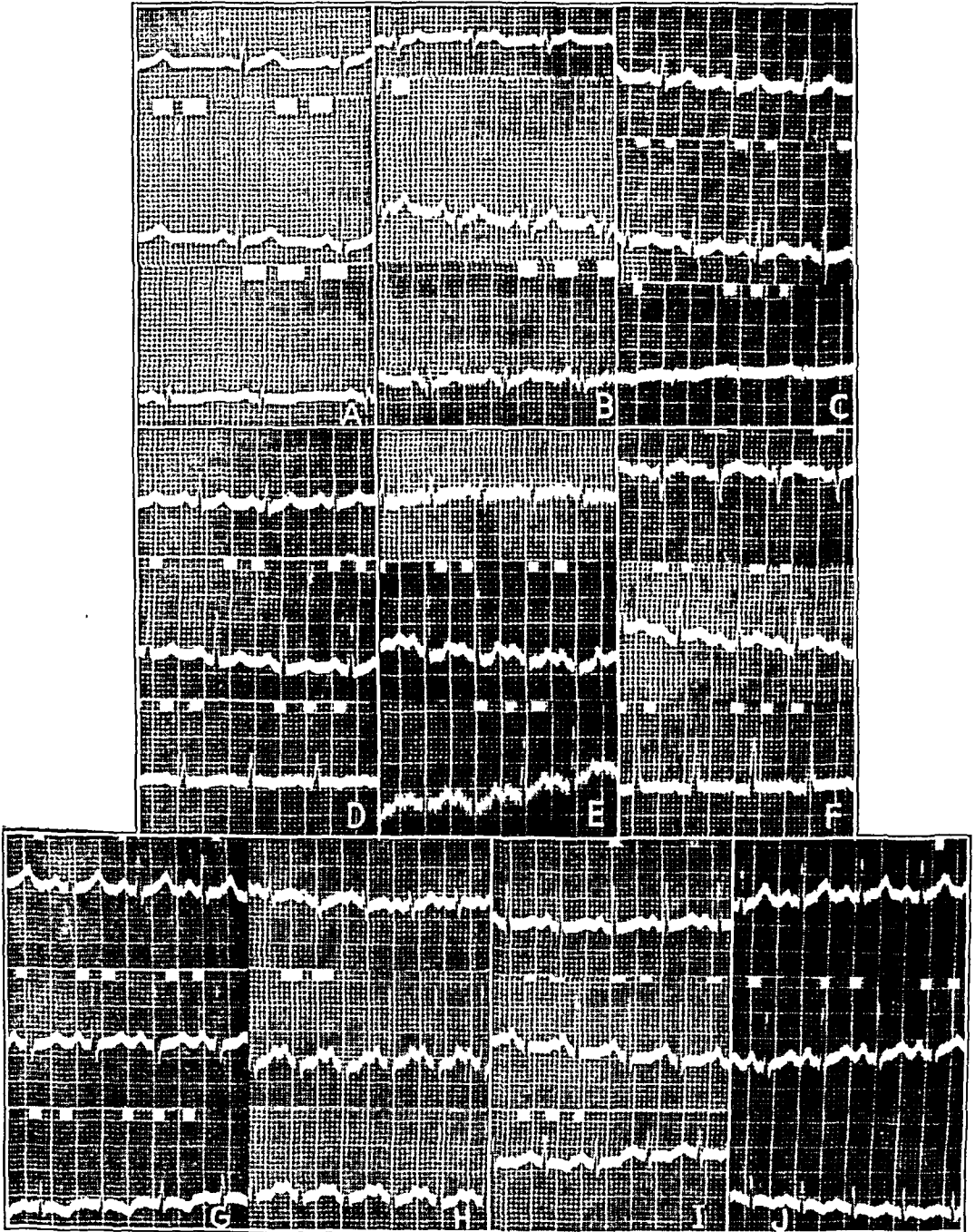


Figure 2

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tion produced myocardial anoxia, and this, in turn, reflexly affected coronary circulation.

Durant, Ginsburg and Roesler<sup>10</sup> stated, on the basis of serial electrocardiograms, that a transient bundle block appeared within two to six hours of pulmonary embolism, with inversion of the T waves in leads II and III and the development of a Q wave in lead III. In those who survive the electrocardiogram soon returns to normal. In experimental work on dogs, it seemed to them that the changes were due to mechanical obstruction and right ventricular dilatation. They noted (as have other observers) the inconstancy of T wave changes in dogs and that section of either the vagus or the sympathetic nerves failed to alter the electrocardiographic patterns in these embolization experiments. Horn, Dack and Friedburg<sup>11</sup> observed the resemblance of myocardial infarction and pulmonary embolism both clinically and electrocardiographically and in a study of 42 cases of pulmonary embolism noted evidence of acute myocardial ischemia in 8. They expressed the belief that right axis deviation, a deep S wave in lead I and a normal T wave in lead III reflected the right ventricular strain occasioned by the pulmonary arterial obstruction and that the myocardial ischemia (evidenced by a Q wave and a cove plane of the RS-T interval in lead III) was due to shock, generalized anoxia (due to reduced pulmonary oxygenation of the blood) and vagal reflexes. They further stated that the increase in tension within the right ventricle diminished the flow through the right coronary artery. Soko-

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10. Durant, T. M.; Ginsburg, I. W., and Roesler, H: *Am Heart J.* **17**:423, 1939.

11. Horn, H.; Dack, S., and Friedburg, C. K.: *Cardiac Sequelae of Embolism of Pulmonary Artery*, *Arch. Int. Med.* **64**:296 (Aug.) 1939.

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#### EXPLANATION OF FIGURE 2

Case 4. *A*, preoperative electrocardiogram, with low voltage of the QRS complex in all leads and a normal axis. *B*, postoperative electrocardiogram, with a normal axis and prominent S waves in leads I and II. *C*, electrocardiogram made twenty-four hours after operation, with preoperative contour.

Case 5. *D*, preoperative electrocardiogram, with a normal axis. *E*, postoperative electrocardiogram, with a prominent S wave in lead I. *F*, electrocardiogram made twenty-four hours after operation, with right axis deviation, elevation of the RT segment in leads II and III and evidence of right ventricular strain. Purulent pericarditis developed later.

Case 6. *G*, preoperative electrocardiogram, with a normal axis and a small S wave in lead I. *H*, postoperative electrocardiogram, with a tendency to a right axis deviation and a prominent S wave in lead I. *I*, electrocardiogram made twenty-four hours after operation, with a normal axis and T waves flattened in all leads. *J*, electrocardiogram made forty-eight hours after operation, with preoperative contour.

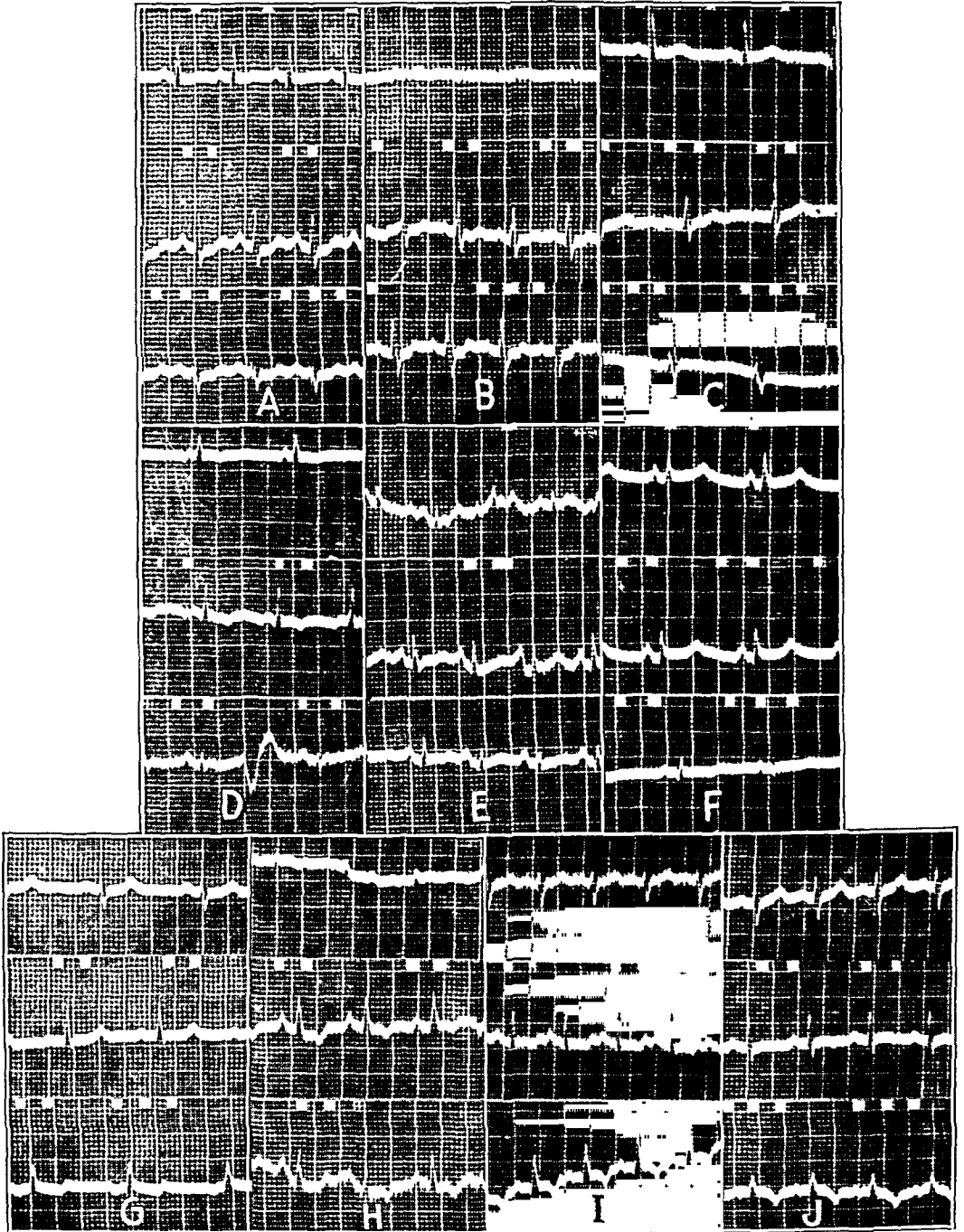


Figure 3

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low, Katz and Muscovitz<sup>12</sup> made a clinical survey of the hospital records of 50 cases and divided the electrocardiograms into four groups, viz., (1) normal curves, (2) those with nonspecific changes, (3) those resembling curves of myocardial infarct and (4) those indicative of cor pulmonale. In the latter two groups, comprising 14 cases, only 5 (10 per cent) corresponded to the McGinn and White type of tracing. These authors were unable to note any characteristic evolution of the curves and were impressed by the transitory nature of the changes, but they did state "deviation of the axis to the right occurred in the majority of cases in which there were control records." The electrocardiographic diagnosis of pulmonary embolus, according to these authors, rested on the absence of the usual curves of a posterior infarct, and the presence of (1) a depressed RS-T interval in lead I and possibly in lead II, (2) low voltage, (3) right axis deviation and (4) a Q wave and an inverted T wave in lead III.

The effect of depressor reflexes and reflex spasm occasioned by the sudden occlusion of the pulmonary artery is well known,<sup>13</sup> but the statements of Fineberg and Wiggers<sup>14</sup> are of interest.

The right ventricle is normally adapted for response to widely different volumes of venous return, but it is not accustomed to react against such great variations in arterial resistance as is the left.

They stated within 58 per cent of pulmonary arterial compression the compensatory mechanism is adequate, and there is "no evidence that

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12. Sokolow, M.; Katz, L. W., and Muscovitz, A. W.: *Am. Heart J.* **19**:166, 1940.

13. de Takats, G.; Beck, W. C., and Fenn, G. K.: *Surgery* **6**:339, 1939. Scherf and Schönbrunner.<sup>7</sup>

14. Fineberg, M. H., and Wiggers, C. J.: *Am. Heart J.* **11**:255, 1936.

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#### EXPLANATION OF FIGURE 3

Case 7. *A*, preoperative electrocardiogram, with a tendency to a left axis deviation. *B*, postoperative electrocardiogram, with a tendency to a right axis deviation and low voltage of the entire complex in lead I. *C*, electrocardiogram made twenty-four hours after operation, with preoperative contour.

Case 8. *D*, preoperative electrocardiogram, with a normal axis, inverted T waves in leads I and II, ventricular extrasystoles in lead III and low voltage throughout. *E*, postoperative electrocardiogram, with a shift of the axis toward the right. *F*, electrocardiogram made twenty-four hours after operation, with a normal axis, an elevated RT segment in leads II and III and early development of a Q wave in lead III. Pericarditis developed later.

Case 9. *G*, preoperative electrocardiogram, with a normal axis and a prominent S wave in lead I. *H*, postoperative electrocardiogram, with a normal axis, low voltage in lead I and inverted T waves in leads II and III. *I*, electrocardiogram made twenty-four hours after operation, with right axis deviation and a prominent S wave in lead I. *J*, electrocardiogram made forty-eight hours after operation, with preoperative contour.

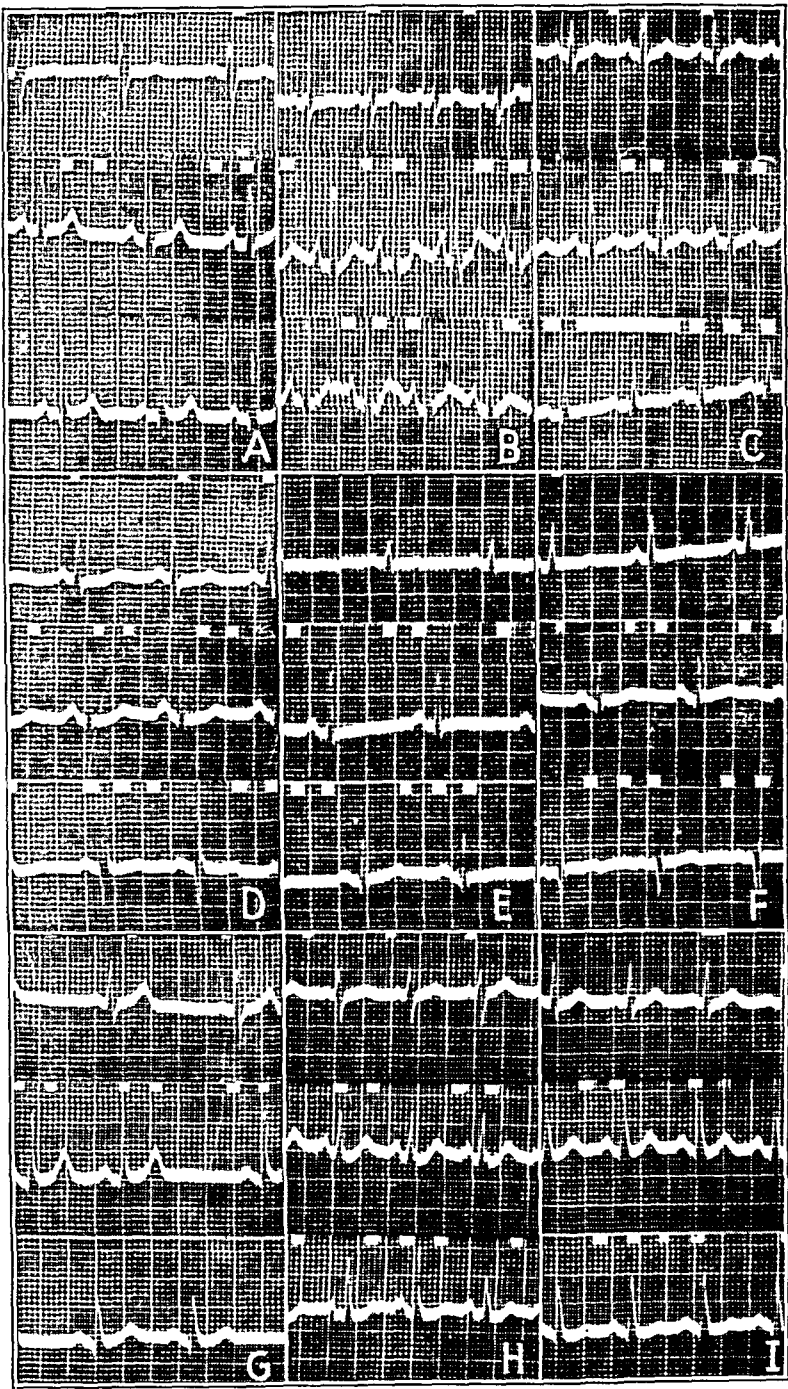


Figure 4

(See legend on opposite page)

circulatory failure following obstruction of the pulmonary circuit has any other cause than failure of the right ventricle." In this connection Gibbon, Hopkinson and Churchill,<sup>15</sup> observing the changes in arterial and venous pressures produced by gradual occlusion of the pulmonary artery in cats, reported that no change occurred until 60 per cent of the artery was occluded and that the failure of the circulation was due to obstruction of the right side of the heart.

Through the cooperation of Dr. H. H. Bradshaw, of the surgical B service of Jefferson Hospital, we were given an opportunity to make serial electrocardiographic studies on patients who were being subjected to lobectomy or pneumonectomy. Tracings were made prior to operation, after induction of anesthesia, after the opening of the thoracic cavity, after the application of a ligature around the artery, after the removal of the lung tissue, after the closure of the chest and at regular intervals until no further changes occurred or the electrocardiogram returned to normal. The anesthetic used in all these operative procedures was a mixture of cyclopropane, oxygen and ether. These studies are of particular significance for two reasons: 1. So far as we know, these are the first reported experimental studies on human beings. 2. The exact time and amount of occlusion could be noted, thus enabling more valid deductions to be drawn from the tracings. It is quite apparent that the method is not wholly comparable to a naturally occurring pulmonary embolus because of the removal of the portion of lung with the obstructed circulation, and hence the absence of pulmonary

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15. Gibbon, J. H., Jr.; Hopkinson, M., and Churchill, E. G.: *J. Clin. Investigation* **11**:543, 1932.

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#### EXPLANATION OF FIGURE 4

Case 10. *A*, preoperative electrocardiogram, with a prominent S wave in lead I and a tendency to a right axis deviation. *B*, postoperative electrocardiogram, with a right axis deviation, a deep S wave in lead I and a staircase ascent of the ST segment in lead II. *C*, electrocardiogram made twenty-four hours after operation, with a return to a normal pattern save for a prominent S wave in lead I.

Case 11. *D*, preoperative electrocardiogram, with a normal axis and a deep Q wave in lead III. *E*, postoperative electrocardiogram, with a normal axis and flat T waves in leads I and II. *F*, electrocardiogram made twenty-four hours after operation, with a return to the preoperative contour save for low voltage throughout.

Case 12. *G*, preoperative electrocardiogram, with a normal pattern. *H*, postoperative electrocardiogram, with a right axis deviation and a prominent S wave in lead I. *I*, electrocardiogram made twenty-four hours after operation, with a return to the preoperative contour.



infarction, but whatever knowledge can be gained from such a procedure seems worthy of scrutiny. It cannot be gainsaid that increased peripheral resistance is offered to the discharge of blood from the right ventricle in these cases. It is also quite apparent that in no case was more than a 55 per cent occlusion presented to the pulmonary flow.

In the accompanying figures are reproduced some of the electrocardiographic tracings and the significant data. Space does not permit

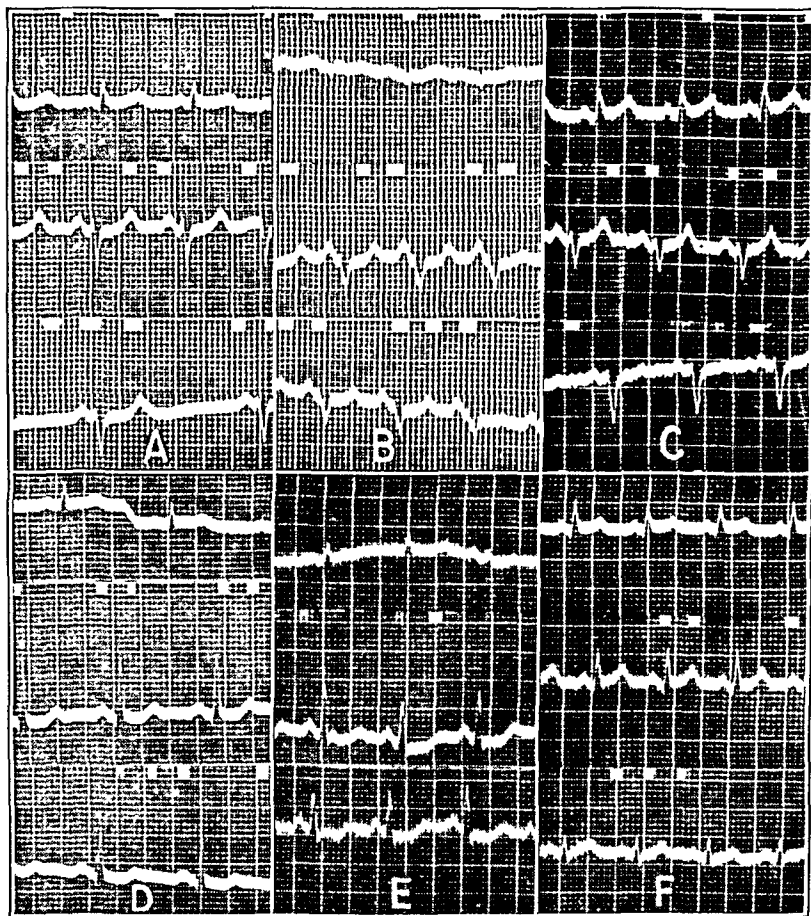


Fig. 5.—Case 13. *A*, preoperative electrocardiogram, with deep S waves in leads II and III, left axis deviation and a sinus pause. *B*, postoperative electrocardiogram, with low voltage in lead I and decreased voltage of the QRS complex throughout. *C*, electrocardiogram made twenty-four hours after operation, with a return to the preoperative contour.

Case 14. *D*, preoperative electrocardiogram, with a normal axis. *E*, postoperative electrocardiogram, with low voltage in lead I and depressed ST segments in leads II and III. *F*, electrocardiogram made twenty-four hours after operation, with a return to practically the same preoperative pattern save for lowered voltage throughout.

the inclusion of the completed series. It was again noted that many different rhythms appeared during the induction of anesthesia, and 1 patient (not included in this report) died at operation of ventricular

standstill. Nowhere in this series was any tracing encountered which resembled that of classic posterior infarct or bundle branch block. Two (cases 1 and 2), or 14.3 per cent, demonstrated changes which might be said to be diagnostic; 4 (cases 3, 6, 10 and 12), or 28.6 per cent, were definitely suggestive, evidencing at least two of the significant alterations; 5 (cases 7, 8, 9, 13 and 14), or 35.7 per cent, showed change of axis alone, and 2 (cases 4 and 5), or 14.3 per cent, had deep S waves in lead I. Ten, or 71.4 per cent, demonstrated a change

*Significant Changes Immediately After and Twenty-Four Hours  
After Operation*

Case No.	Portion of Lung Removed	Right Axis, Deviation or Tendency	Development of S <sub>1</sub> Staircase Ascent of RS-T Segment			Twenty-Four Hours After Operation
			With or Without S <sub>2</sub>			
1	Lower lobe of left lung.....	Tendency	+	+		Return to preoperative contour
2	Right lung.....	Tendency	+	+		S <sub>1</sub> persistent
3	Right lung.....	—	+	+		Lowered voltage
4	Middle and lower lobes of left lung	—	—	+		Return to preoperative contour
5	Left lung.....	—	—	+		Pericarditis and right ventricular strain
6	Left lung.....	Tendency	—	+		Return to preoperative contour
7	Lower lobe of right lung.....	Deviation	—	—		Return to preoperative contour
8	Right lung.....	Deviation	—	—		Pericarditis
9	Middle and upper lobes of right lung	Tendency	—	—		Right ventricular strain
10	Left lung.....	Tendency	+	—		Return to preoperative contour
11	Left lung.....	—	—	—		Lowered voltage
12	Lower lobe of left lung.....	Tendency	—	+		Return to preoperative contour
13	Left lung.....	Tendency (?)	—	—		Return to preoperative contour
14	Left lung.....	Tendency	—	—		Lowered voltage

of electrical axis to the right. Of the 14 electrocardiograms, only 1 (case 11), was considered to show alteration of a nonspecific character, namely, flattening of the T waves in all leads. In cases 5 and 8 pericarditis developed postoperatively, and the tracings reproduced demonstrate the elevation of the RS-T segments in leads II and III in both cases, although a Q wave in lead III was seen only in case 8. Summarized from the view of usefulness in diagnosis, 2 electrocardiograms were diagnostic, 7 were highly suggestive (failure of serial tracings to develop the pattern expected in coronary occlusion would go far to help establish a diagnosis), 4 had changes which could be intelligently and usefully interpreted only when compared with prior

tracings and only 1 showed alterations which would be considered noncontributory toward the establishment of a diagnosis. These selections have been made arbitrarily, only from the tracings taken immediately after the operation, since no further diagnostically significant changes appear thereafter. Within twenty-four hours, in 10 cases, tracings returned to the preoperative pattern (though lowered voltage was evident in 3). In 1 case evidence of right ventricular strain persisted for forty-eight hours; in 2 cases the electrocardiographic changes of pericarditis were seen, and in 1 (case 2) there was persistence of the S wave in lead I.

Scrutiny of the assembled material demonstrates no correlation in this study between age, sex, site and extent of the occlusion or previous electrocardiographic pattern and development of electropotential changes. The fact that 71.4 per cent of the electrocardiograms presented evidence of axis shift to the right must be taken as evidence of strain placed on the right ventricle, since in 6 of the 10 showing this change operation was performed on the left hemithorax. The next most frequently observed change was the appearance of an S wave in lead I, and this further supports the view of McGinn and White. In none of the 14 cases studied was there immediately after operation a change in the Q and T waves in lead III, the T wave changes apparently being entirely nonspecific except in the 2 cases (5 and 9) of frank right ventricular strain. The evidence in these tracings indicates that change occurs immediately after occlusion and usually disappears within twenty-four hours. It should again be emphasized that in no case was there an obstruction of more than 55 per cent of the pulmonary circulation.

#### SUMMARY

An electrocardiographic study is presented of 14 cases of acute pulmonary artery occlusion in human beings incident to partial or complete unilateral pneumonectomy.

The significant changes in the electrocardiographic pattern produced by acute pulmonary artery occlusion in this study are: (1) shift of the electrical axis to the right, 71.4 per cent; (2) development of a deep S wave in lead I, 50 per cent, and (3) staircase ascent of the RS-T segment in lead II, 28.6 per cent. These changes tend to appear immediately after the occlusion and to disappear within twenty-four hours, but not constantly so.

The nature of the changes observed are such as to lend support to the belief that electrocardiographic changes associated with pulmonary embolism are produced by strain placed on the right ventricle.

Proper use and interpretation of electrocardiograms, bearing in mind their limitations, may be of help in differentiating pulmonary embolism at its onset from clinically similar diseases.

# EFFECT OF INFLAMMATION ON THE CONCENTRATION OF SULFANILAMIDE IN PLEURAL AND JOINT FLUIDS

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Marshall, Emerson and Cutting<sup>1</sup> have emphasized that the distribution of sulfanilamide is essentially equal in all the tissues of the body with the exception of bone and fat. They called attention to the slightly lower concentration of this substance in the saliva and pancreatic juice of the dog and in the spinal fluid of man as compared with its level in the blood.

These workers studied the concentration of sulfanilamide in pleural fluid in a few instances. They found, for example, a level of 7.4 mg. of drug per hundred cubic centimeters of pleural exudate in a case of streptococcic empyema, with a corresponding blood level of 9.3 mg. per hundred cubic centimeters. In another case they found 11 mg. per hundred cubic centimeters in a pleural effusion from a patient to whom 0.10 to 0.12 Gm. of drug per kilogram of body weight was being administered daily. In a second paper these investigators<sup>2</sup> referred again to the aforementioned case of pleural effusion, of undesignated cause, as well as to the case of a patient with hemolytic streptococcic empyema who was receiving 2.4 Gm. of sulfanilamide daily and who had a level of 3.5 mg. of the drug per hundred cubic centimeters of pleural exudate.

Apparently but little attention has been paid to the passage of sulfanilamide into fluids of inflammatory origin. Some authors<sup>3</sup> have used sulfanilamide in the treatment of empyema but have not mentioned the concentration of the drug in the pleural exudate.

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1. Marshall, E. K., Jr.; Emerson, K., Jr., and Cutting, W. C.: The Distribution of Sulfanilamide in the Organism, *J. Pharmacol. & Exper. Therap.* **61**:196, 1937.

2. Marshall, E. K., Jr.; Emerson, K., Jr., and Cutting, W. C.: Paraaminobenzenesulfonamide: Absorption and Excretion; Method of Determination in Urine and Blood, *J. A. M. A.* **108**:953 (March 20) 1937.

3. Lester, C. W.: Sulfanilamide and Prontosil in the Treatment of Hemolytic Streptococcus Empyema in Children, *Am. J. Surg.* **43**:153, 1939. Oetken, H.: Uliron bei Meningokokken-Meningitis und post-pneumonischen Pneumokokkenpleuraempyem, *Deutsche med. Wchnschr.* **64**:1683, 1938. Gay, F. P., and Clark, A. R.: On the Mode of Action of Sulfanilamide in Experimental Streptococcus Empyema, *J. Exper. Med.* **66**:535, 1937.

As just noted, Marshall and associates reported the levels of the drug in the pleural fluid in 1 case of streptococcic empyema and 1 case of pleural effusion. The levels were 7.4 and 11 mg. per hundred cubic centimeters, respectively. These values were close to the respective blood levels. Leahy<sup>4</sup> reported values for sulfanilamide in the pleural fluid in 2 of 7 cases of streptococcic empyema in which treatment was with this drug. The estimations were limited to one in each of the 2 cases, and the results per hundred cubic centimeters were 4.6 and 2.7 mg. in the blood and 2.9 and 3.0 mg. in the pleural fluid, respectively.

Two well known monographs<sup>5</sup> on the subject of sulfanilamide and related compounds had little or nothing to say regarding the accumulation of sulfanilamide in pleural fluid.

The results I have obtained from a study of the level of sulfanilamide in the blood and that in pleural fluid of patients with acute tuberculous pleural effusion have shown a great difference between the two. These results indicate that an inflammatory reaction may greatly influence the local concentration of sulfanilamide.

#### MATERIAL AND METHOD

Five patients with proved acute tuberculous pleural effusion or a clinical diagnosis of such disease served as the subjects of six serial studies. All patients were acutely ill with fever. The cause of the pleural effusion was proved to be the tubercle bacillus in 4 cases. From the nature of the fluid and the clinical course of illness the effusion appeared to be tuberculous in the fifth patient studied, although tubercle bacilli were not found. In addition, 1 patient with acute and 1 with chronic inflammatory joint disease served as subjects.

The drug was given in a large initial dose, such as 4 or 5 Gm. (60 to 75 grains), and in doses of 15 to 20 grains (1 to 1.3 Gm.) at four hour intervals thereafter.

The levels of sulfanilamide in the blood, pleural fluid and joint fluid were estimated by the method of Marshall, Emerson and Cutting.<sup>2</sup>

#### RESULTS

The results of the study are recorded in tables 1 and 2. The striking general fact is that in all instances the pleural fluid was found to contain at some time an amount of sulfanilamide much greater than that in the blood. The patient with the acute inflammatory disease of a joint also

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4. Leahy, L. J.: The Use of Sulfanilamide in the Treatment of Hemolytic Streptococcic Empyema, *New York State J. Med.* **40**:347, 1940.

5. Long, P. H., and Bliss, E. A.: The Clinical and Experimental Use of Sulfanilamide, Sulfapyridine and Allied Compounds, New York, The Macmillan Company, 1939. Mellon, R. R.; Gross, P., and Cooper, F. B.: Sulfanilamide Therapy of Bacterial Infections, Springfield, Ill., Charles C. Thomas, Publisher, 1938.

showed a marked increase of the drug in the joint fluid as compared with the level in the blood. In patient A. B. the pleural fluid level of sulfanilamide reached 66.6 mg. per hundred cubic centimeters, approximately six times the concentration in the blood. The marked disparity in the levels of the drug is shown in this case by the presence of a slight trace in the blood and a concentration of 44.4 mg. per hundred cubic centimeters in the pleural fluid. In patient H. H. the respective levels of 7.1 and 133.3 mg. per hundred cubic centimeters of blood and of pleural fluid showed a nineteenfold increase in the concentration of the drug in the pleural fluid.

It is difficult to explain some of the results. For example, in patient A. B. on May 30 the blood contained none and the pleural fluid only a trace of the drug. Four days later, however, the blood showed a slight trace and the pleural fluid 44.4 mg. per hundred cubic centimeters. The drug had been discontinued eight days previously. The factor of concentration of the drug in the pleural fluid by absorption of water may be the explanation. This factor was not rigidly controlled. However, frequent physical and roentgen ray examinations of the chest and general clinical knowledge of the case did not indicate rapid absorption of fluid.

The rapidity with which the marked concentration of the drug occurs in the pleural fluid is shown in all 5 cases studied. In patient A. B. the pleural fluid level was more than double the blood value five hours after the initial dose. In patient H. H. the pleural fluid level was eight times the blood level of the drug within three hours after the initial dose. In this instance one would have expected a higher blood level of the drug on the basis of the amount given. The rapid accumulation of the drug in the pleural fluid probably prevented the blood level from rising as it would have done in the absence of the pleural fluid. In the case of J. J. this point is further emphasized by the fact that the pleural fluid level was more than fifteen times the blood level one hour after an initial dose of 75 grains (4.9 Gm.). In the instance of the first admission of patient R. R., the level of sulfanilamide in the pleural fluid was double that in the blood within three hours after the initial dose. A much more rapid diffusion of the drug into the pleural fluid was shown during the second admission of the same patient, at which time the amount of sulfanilamide in the pleural fluid was four times the blood level of the drug one hour after the initial dose. This patient was severely ill, with high fever, at the time. This was interpreted as probably indicating a greater inflammatory reaction in the pleura at the time of the second admission.

In 3 patients, A. B., J. S. and R. R. on the first admission, in whom the concentration of sulfanilamide in the pleural fluid did not rise so quickly to high levels, the initial blood values of the drug, up to four

TABLE 1.—*Comparison of the Blood and Pleural Fluid Levels of Sulfanilamide in Five Cases of Acute Tuberculous Pleurisy with Effusion*

Patient	Date	Hour	Sulfanilamide Dosage	Concentration of Sulfanilamide, Mg. per 100 Cc.	
				Blood	Pleural Fluid
A. B.....	5/24	10:00 a. m.	60 grains		
	5/24	2:00 p. m.	20 gr. every 4 hr.		
		3:00 p. m.	.....	11.7	27.4
	5/25	11:30 a. m.	15 gr. every 4 hr.	10.9	50.0
	5/26	.....	Drug stopped		
	5/27	9:30 a. m.	.....	11.1	66.6
	5/30	10:00 a. m.	.....	None	Trace
	6/ 3	1:00 p. m.	.....	Slight trace	41.4
	6/10	.....	.....	None	None
H. H.....	5/17	3:00 p. m.	60 gr.		
	5/17	6:15 p. m.	15 gr. every 4 to 6 hr.		40
	5/18	10:30 a. m.	Same	10	10
	5/19	9:00 a. m.	Last dose at 8 a. m.; total dose 160 gr.	10	10
	5/24	3:00 p. m.	.....	None	33.3
	5/30	4:00 p. m.	.....	None	72.7
	6/ 3	1:00 p. m.	.....	7.1	133.3
	6/ 6	.....	.....	None	None
J. S.....	5/ 9	10:00 a. m.	50 gr.		
	5/ 9	2:00 p. m.	20 gr. every 4 hr.		
	5/ 9	4:45 p. m.	.....	10.2	8.8
	5/10	3:00 p. m.	20 gr. every 4 hr.	13.3	15.3
	5/14	4:00 a. m.	Last dose 20 gr.		
	5/14	12 noon	.....	14.3	15.3
	5/17	.....	.....	10.0	40.0
	5/24	3:00 p. m.	.....	None	40.0
	5/30	3:15 p. m.	.....	None	40.0
	6/ 3	1:00 p. m.	.....	None	38.0
	6/10	.....	.....	None	None
J. J.; tuberculous pericarditis with effusion, as well as pleural effusion	1/11	11:00 a. m.	75 gr.		
	1/11	12 noon	.....	4	66.6
	1/11	1:00 p. m.	.....	5	72.7
	1/11	2:00 p. m.	.....	6.2	88
	1/11	3, 7 and 11 p. m.	15 gr.	7.0	114.2
	1/12	3 and 7 a. m.	15 gr.		
	1/12	6:00 p. m.	.....	5.0	23.0
	1/12	6:00 p. m.	.....	(Pericardial fluid, 8.3 mg.)	
	1/17	12 noon	.....	None	53.3
	1/21	.....	.....	Slight trace	36.3
	1/24	.....	.....	5.8	29.6
	1/27	.....	.....	None	36.3
	2/ 2	.....	.....	4.0	58.8
	2/ 7	.....	.....	14.2	Bare trace
	2/12	.....	.....	None	Trace
First Admission					
R. R.....	12/13	8:00 a. m.	75 gr.		
	12/13	9:00 a. m.	.....	8.5	8.7
	12/13	10:00 a. m.	.....	11.4	9.5
	12/13	11 a. m. and 2, 5, 8 and 11 p. m.	15 gr.	11.7	22.2
	12/13	12 noon	.....	12.5	25.0
	12/13	3:00 p. m.	.....	7	5.2
	12/13	6:00 p. m.	.....	5	17.3
	12/14	9:00 a. m.	.....	4.4	5.8
	12/15	9:00 a. m.	.....	Faintest trace	34.4
	12/16	11:00 a. m.	.....	None	42.1
	12/17	10:45 a. m.	.....	None	32.8
	12/17	10:45 a. m.	.....	(700 cc. pleural fluid removed)	
	12/19	12:45 p. m.	.....	Not examined	38.0
	12/21	11:00 a. m.	.....	None	44.4
	12/23	11:00 a. m.	.....	None	100
	12/26	1:00 p. m.	.....	None	15.1
	12/29	11:00 a. m.	.....	None	33.3
	12/31	11:00 a. m.	.....	None	51.9
	1/ 3	11:00 a. m.	.....	Slightest trace	Small trace
	1/11	11:00 a. m.	.....	None	None

TABLE 1.—*Comparison of the Blood and Pleural Fluid Levels of Sulfanilamide in Five Cases of Acute Tuberculous Pleurisy with Effusion—Continued*

Patient	Date	Hour	Sulfanilamide Dosage	Concentration of Sulfanilamide, Mg. per 100 Cc.	
				Blood	Pleural Fluid
Second Admission					
R. R.; returned	1/17	12 noon	75 gr.		
several days after	1/17	1:00 p. m.	.....	9.5	36.3
discharge, with	1/17	2:00 p. m.	.....	9.5	44.4
marked evidence	1/17	3:00 p. m.	.....	9.2	40.0
of increase in	1/17	4 and 8 p. m. and	15 gr.	9.5	50.0
fluid in chest,		12 midnight			
fever and much	1/18	4 and 8 a. m.	15 gr.		
greater degree	1/18	.....	.....	6.6	8.4
of illness than	1/21	.....	.....	Bare trace	34.7
on first admis-	1/24	.....	.....	3.2	80.0
sion	1/27	.....	.....	None	33.3
	2/ 2	.....	.....	8.8	64.5
	2/ 7	.....	.....	Trace	57.1
	2/13	.....	.....	None	3.5

hours after the initial large dose, were about 10 mg. per hundred cubic centimeters. This is the amount usually seen under such circumstances. In 2 other patients, however, H. H. and J. J., in whom the concentration of sulfanilamide in the pleural fluid quickly reached high levels, the blood level of the drug was only about half that usually found after the amount of the drug which was given. This apparent capacity of large inflammatory exudates to prevent the attainment of a desirable blood level of the drug may be an important consideration in the treatment of some patients. On the other hand, the apparent tendency of sulfanilamide to become selectively concentrated in fluids of inflammatory origin may raise the question whether relatively much smaller doses than those usually employed would not suffice to bring the concentration in the area of inflammation to an effective level. It is obvious that this speculation would not apply in cases of septicemia.

The length of time that the high levels of sulfanilamide remained in the pleural fluid is of interest. In patient J. J. the pleural fluid level of the drug was 58.8 mg. per hundred cubic centimeters twenty-one days after the drug was discontinued. In patient R. R. it was 100 mg. ten days after and 51 mg. per hundred cubic centimeters eighteen days after discontinuation of the drug. Twenty-one days after the drug was discontinued only a small trace remained in the pleural fluid. On the second admission of patient R. R. the level of sulfanilamide in the pleural fluid was 57 mg. per hundred cubic centimeters twenty days after and 3.5 mg. twenty-nine days after discontinuation of the drug. In the case of A. B. 44.4 mg. of sulfanilamide per hundred cubic centimeters remained in the pleural fluid ten days after the drug was stopped. It disappeared from the pleural fluid within seven more days. Patient H. H. showed the high value of 133 mg. of the drug per hundred cubic centimeters of pleural fluid fifteen days after the drug was stopped, but none three days later, i. e., eighteen days after discontinuation of the



drug. J. S. showed 38 mg. of sulfanilamide per hundred cubic centimeters of pleural fluid twenty days after discontinuation of the drug. Within another week the drug had disappeared from the pleural fluid. In general, the results in the few cases studied indicate that sulfanilamide may remain in the pleural fluid at high levels two to three weeks after the drug is stopped.

The large amounts present in the pleural fluid, and perhaps in other fluids as well, may serve as the source from which the blood level of the drug may again reach a considerable figure. This is shown by the following data: On May 24 and May 30 sulfanilamide was not found in the blood of patient H. H. On June 3, however, the blood value was 7.1 mg. per hundred cubic centimeters. In the case of patient J. J. there was no sulfanilamide in the blood on January 17, a slight trace

TABLE 2.—*Comparison of the Blood and Joint Fluid Levels of Sulfanilamide in a Case of Acute Purulent Effusion of the Left Knee of Undefined Cause and a Case of Chronic Gonococcic (?) Arthritis of the Right Elbow*

Patient	Date	Hour	Sulfanilamide Dosage	Concentration of Sulfanilamide, Mg. per 100 Cc.	
				Blood	Fluid from Joint
J. J.....	6/10	8:00 a. m.	75 grains		
	6/10	12 noon	.....	5.2	27
	6/12	2:00 p. m.	.....	None	228
	6/15	1:00 p. m.	.....	1.7	88
	6/20	8:00 p. m.	.....	None	None
W. F.....	5/ 5	9:30 a. m.	80 grains		
	5/ 5	12:30 a. m.	20 grains		
	5/ 5	3:00 p. m.	.....	11	11.5
	5/ 6	2:00 p. m.	.....	14	13.8
	5/ 9	4:30 p. m.	.....	Trace	Trace

on January 21, 5.8 mg. per hundred cubic centimeters on January 24, none on January 27, 4.0 mg. on February 2 and 14.2 mg. on February 7. The blood of patient R. R. showed similar changes on the second admission. These results indicate that it is necessary to bear in mind the possibility of reabsorption of the drug from large exudates, particularly with reference to continued or renewed administration. It would obviously be possible to exceed the limit of safe blood levels of the drug if absorption both from the gastrointestinal tract and from an inflammatory exudate occurred simultaneously. This is further evidence of the desirability for control of therapy by frequent estimations of the blood levels of sulfanilamide.

Table 2 shows the results obtained in 2 cases of joint effusion. Patient J. J. presented all the clinical evidence of acute purulent arthritis. The localization in one large joint, the purulent nature of the fluid, the extreme tenderness, the local redness, the swelling, etc., were responsible for a clinical diagnosis of acute gonococcic arthritis. The etiologic agent was never proved bacteriologically. It may be seen

from table 2 that on June 12, two days after a single dose of 75 grains (4.9 Gm.) of sulfanilamide, the level of the drug in the joint fluid was unusually high, 228 mg. per hundred cubic centimeters. The drug was not detectable in a sample of blood taken at the same time as the joint fluid. Five days later the level of sulfanilamide in the joint fluid was still 88 mg. per hundred cubic centimeters and that in the blood 1.7 mg. This shows the extreme degree to which this drug may become concentrated in an acutely inflamed area.

Data for patient W. F., on the contrary, show what may occur in a case of chronic inflammation of a joint (table 2). This patient came to the hospital complaining of a swollen right elbow. This joint had become acutely tender, swollen and red for the first time about six months before admission to the hospital. The joint was not tender at the time of admission, but it was almost useless because of marked destruction of the joint cartilage. There was a history of an episode of acute gonorrheal urethritis which had preceded the initial symptoms in the joint by several weeks. A urethral smear was positive for gonococci while the patient was in the hospital. The joint fluid was viscous and opalescent and had a high protein content, but no cellular elements were seen on microscopic study.

Reference to the table will show that the levels of sulfanilamide in the joint fluid of W. F. were practically identical with those found in the blood on three occasions. This is probably due to the fact that the inflammation had completely subsided and the capillary permeability, which is increased in acutely inflamed areas, had again returned to normal.

#### COMMENT

The marked increase of the level of sulfanilamide in the pleural fluid over that in the blood shown in the six serial studies of 5 patients with acute inflammation of the pleura is no doubt due to the increase in permeability of capillaries well known to accompany acute inflammation. It is interesting to speculate whether there may be a similar increase in the concentration of this and related drugs when they are used in the treatment of such diseases as streptococcic empyema and streptococcic and meningococcic meningitides. It seems reasonable to predict that the same marked increase in the concentration of the drug over the level in the blood may be found in the inflamed areas, if a sufficient number of observations are made.

It is also desirable to speculate whether this same increase may not occur in localized areas of inflammation, such as are associated with pneumonia and cellulitis. It seems unlikely, however, that the increased level in the acutely inflamed area would persist any length of time after the drug was discontinued. One may also wonder, on the basis of evidence

presented, whether it is not possible to attain bacteriostatic concentrations of the drug, i. e., 10 to 15 mg. per hundred cubic centimeters, in inflamed tissue without the same high level in the blood. This consideration would obviously not apply in cases of septicemia. If such is the case, it would have an important bearing on the possibility of decreasing the toxic, and even fatal, effects of sulfanilamide and related substances. It may also explain the satisfactory therapeutic results often observed with a relatively low blood level.

#### SUMMARY AND CONCLUSIONS

The results of the study of the concentration of sulfanilamide in the acute inflammatory pleural exudate of 5 patients on six occasions and in the joint fluid in 1 case of acute and 1 case of chronic arthritis with effusion are presented. The results are discussed from the point of view that possibly a lower than currently accepted blood level of sulfanilamide may suffice to produce a concentration of the drug in the inflamed areas sufficiently high to achieve the necessary results. The possible decrease in the toxic effects resulting from a lower blood level is mentioned.

# SHORT PR INTERVAL ASSOCIATED WITH A PROLONGED QRS COMPLEX

A CLINICAL AND EXPERIMENTAL STUDY

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Twelve years ago Wolff, Parkinson and White<sup>1</sup> described a syndrome appearing in healthy young people subject to attacks of paroxysmal tachycardia. Electrocardiograms taken during the intervals between attacks showed wide QRS complexes with short PR intervals. Isolated cases had been previously reported by Wilson,<sup>2</sup> Wedd<sup>3</sup> and Hamburger,<sup>4</sup> but the complete picture had not been appreciated. This syndrome, though uncommon, is now well known,<sup>5</sup> and it is recognized that the bizarre electrocardiograms do not necessarily represent cardiac damage. It occurs in all age groups with the exception that it has not yet been recognized in a newborn infant. It is more common in males, and most persons have attacks of paroxysmal tachycardia of either supraventricular or ventricular origin. In some of the cases reported atropine or exercise has caused the electrocardiographic pattern to return to a normal configuration, but this is not an invariable finding. A recent

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1. Wolff, L.; Parkinson, J., and White, P. D.: Bundle Branch Block with Short P-R Interval in Healthy Young People Prone to Paroxysmal Tachycardia, *Am. Heart J.* **5**:685 (Aug.) 1930.

2. Wilson, F. N.: A Case in Which the Vagus Influenced the Form of the Ventricular Complex of the Electrocardiogram, *Arch. Int. Med.* **16**:1008 (Dec.) 1915.

3. Wedd, A. M.: Paroxysmal Tachycardia, with Reference to Nomotropic Tachycardia and the Role of the Extrinsic Cardiac Nerves, *Arch. Int. Med.* **27**:571 (May) 1921.

4. Hamburger, W. W.: Bundle Branch Block: Four Cases of Intraventricular Block Showing Some Interesting and Unusual Clinical Features, *M. Clin. North America* **13**:343 (Sept.) 1929.

5. Bishop, L. F., Jr.: Bundle Branch Block with Short P-R Interval in Individuals Without Organic Heart Disease: Case Report with Review of Literature, *Am. J. M. Sc.* **194**:794 (Dec.) 1937.

paper by Hunter, Papp and Parkinson<sup>6</sup> gave a good review of the subject and listed the numerous mechanisms that have been suggested to explain this phenomenon.

Many of these hypotheses have been ingenious and complicated, and none has ever been definitely proved. One group of investigators has suggested that the electrocardiographic changes represent true bundle branch block, while a larger group has expressed the belief that it is only an apparent bundle branch block due to a ventricular asynchronism, with premature stimulation and contraction of one ventricle.

#### CLINICAL STUDY

We first became interested in this problem about three years ago when we observed a typical case of the syndrome in a 68 year old woman who came to the clinic because of episodes of paroxysmal tachycardia of three years' duration. Her attacks had become increasingly frequent during the preceding year and at the time of admission often occurred ten times a day. There was no previous history of heart disease. A complete cardiac examination revealed that the patient probably had early arteriosclerotic heart disease, consistent with her age. There was no hypertension or angina pectoris, and there had been no evidence of cardiac failure.

Figure 1 shows the electrocardiograms of this patient made during an attack of paroxysmal tachycardia, during normal rhythm and at a time when the PR interval was short and the QRS complex was prolonged. The last type of pattern would disappear from time to time but was not definitely influenced by atropine or vagal pressure. The attacks of paroxysmal tachycardia were controlled by quinidine sulfate, and she has remained free of cardiac symptoms for three years. During the past eighteen months her electrocardiograms have consistently shown a short PR interval and a prolonged QRS complex. Esophageal electrocardiograms showed similar changes.

In an incomplete study of our files we have found 4 cases of a similar condition, 1 of which<sup>7</sup> has been reported previously. The case of a 25 year old stenographer (fig. 2) is interesting in many respects. This patient first reported to the clinic in 1925, at the age of 9 years. She had no particular complaints, but a routine electrocardiogram showed

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6. Hunter, A.; Papp, C., and Parkinson, J.: The Syndrome of Short P-R Interval, Apparent Bundle Branch Block, and Associated Paroxysmal Tachycardia, *Brit. Heart J.* **2**:107 (April) 1940.

7. Sigler, L. H.: Functional Bundle Branch Block (Partial) Paradoxically Relieved by Vagal Stimulation, *Am. J. M. Sc.* **185**:211 (Feb.) 1933.

an unusual type of tracing; she was considered to have heart disease and was followed intermittently in the cardiac clinic. A recent electrocardiogram (fig. 2 *B*) showed the short PR intervals and wide QRS complexes typical of this syndrome. Slurring of the initial QRS deflection, which is a common observation, was present. A review of the history

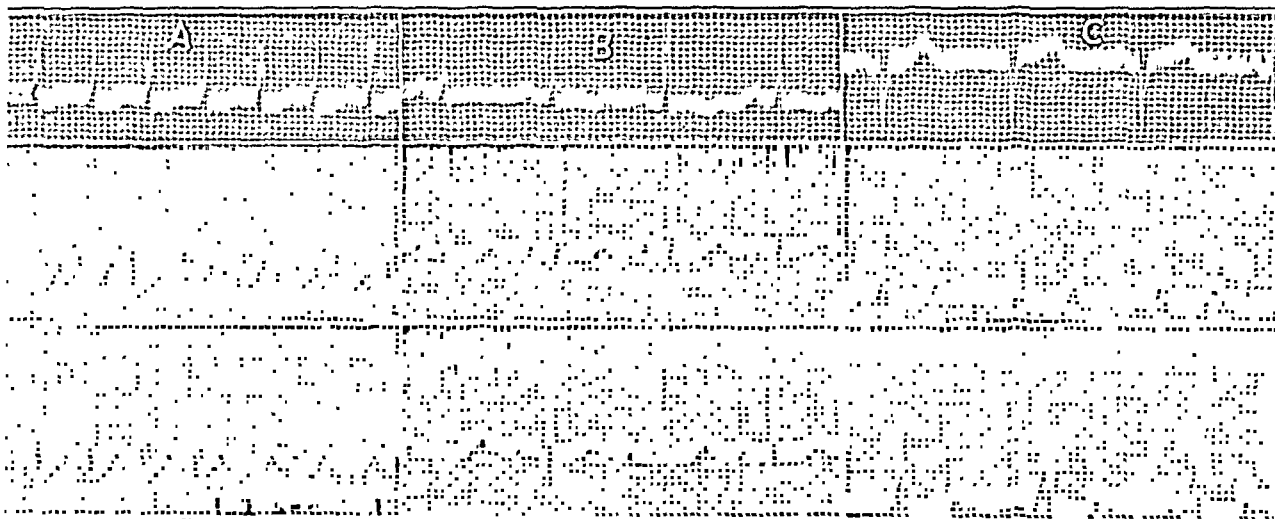


Fig. 1 (patient E. S., a 68 year old woman).—*A*, standard leads during an attack of paroxysmal tachycardia. *B*, normal complexes. *C*, standard leads with short PR intervals and wide QRS complexes.

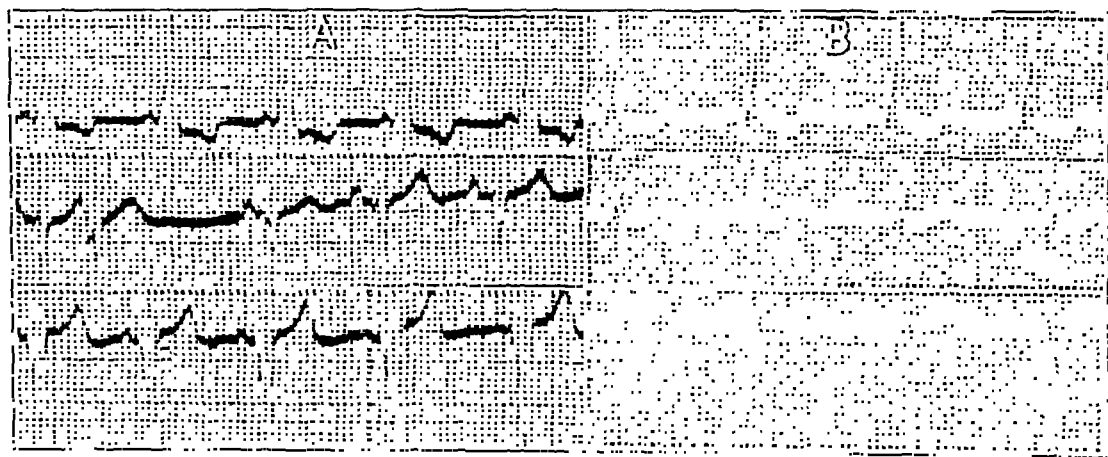


Fig. 2 (patient T. B.).—*A*, standard leads taken in 1925, at the age of 9 years. *B*, standard leads taken in 1940, at the age of 24 years. All tracings show short PR intervals with wide QRS complexes.

and physical findings of this patient showed that aside from episodes of palpitation there was no evidence of organic heart disease. She was somewhat apprehensive because she had been attending the cardiac clinic for sixteen years. A search of our old files brought to light the original electrocardiogram (fig. 2 *A*), taken in 1925. A comparison with the

tracing taken in 1940 (fig. 2 *B*) will show that exactly the same configuration was present on both occasions and had probably been present before this time—possibly since birth. Unfortunately, we have never been able to study this girl when she was complaining of palpitation.

An extremely interesting occurrence in both of these cases (fig. 3) was the presence of occasional premature auricular contractions in which the P waves were of a different character but the QRS complexes remained practically unchanged.

#### EXPERIMENTAL STUDY

To continue this study we turned to animal experimentation. Our first attempts were concerned with the formation of a new conduction pathway between the auricles and ventricles. This was done in cats and

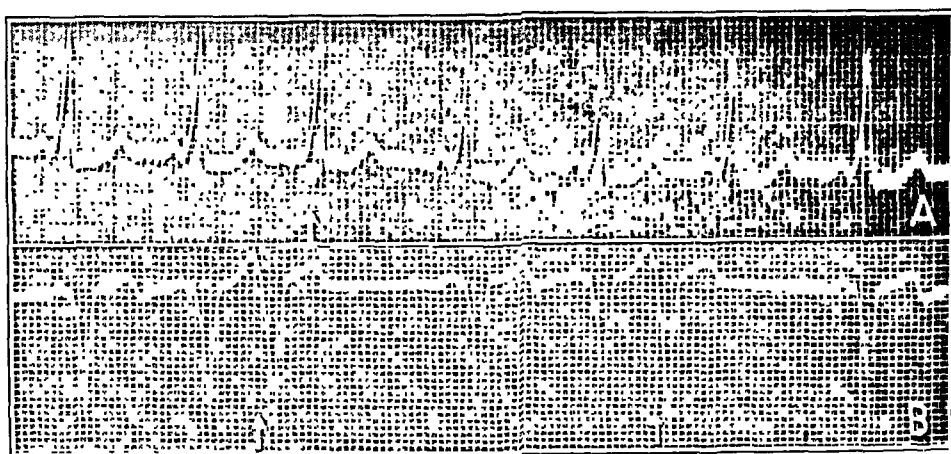


Fig. 3.—Auricular extrasystoles (marked by arrows) interrupting the regular rhythm. The QRS complexes remain relatively unchanged. *A*, patient E. S., lead II. *B*, patient T. B., lead III.

dogs. Anesthesia with pentobarbital sodium and artificial respiration through a tracheal cannula were induced; the heart was exposed, and an auricular appendage was connected to the corresponding ventricle by platinum wire, by needles, by wick bridges soaked in physiologic solution of sodium chloride and by suturing. These attempts were unsuccessful in producing any electrocardiographic changes, and we have since been informed by Dr. C. C. Wolferth<sup>8</sup> that similar experiments by himself and Dr. T. M. MacMillan several years ago yielded negative results.

We next used an amplifier<sup>9</sup> to produce electrically an abnormal conduction pathway between the auricles and ventricles. The current

8. Wolferth, C. C.: Personal communication to the authors.

9. Bell & Howell Company lent us a standard amplifier, and Mr. Fred Brethauer and Mr. Bruce Beasley, of that company, assisted us.

generated by the auricular muscle was picked up by small silver electrodes placed directly on the surface of the auricle. This current was then amplified several thousand times and used to stimulate one ventricle by means of similar electrodes placed on the ventricular epicardium or in



Fig. 4 (cat 12).—Standard leads showing normal complexes and complexes with a short PR interval and a wide QRS group. The time during which the amplifier was turned on is indicated by the black base line.

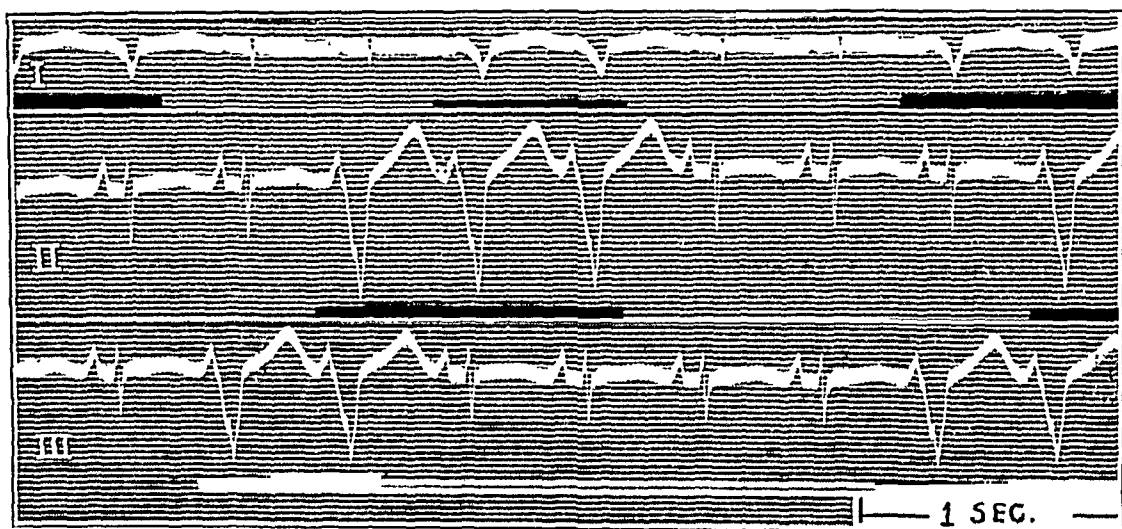


Fig. 5 (cat 12).—Standard leads showing normal complexes and complexes with a short PR interval and a wide QRS group. The time the amplifier was turned on is indicated by the black base line.

the ventricular muscle. Many difficulties were encountered because of feedback and alternating current interference, but these were eliminated by slight modifications of the amplifier.



The time delay in the amplifier was negligible, and in this manner we were able to short circuit the normal conduction systems of cat and dog hearts, which requires six to eight hundredths of a second for an

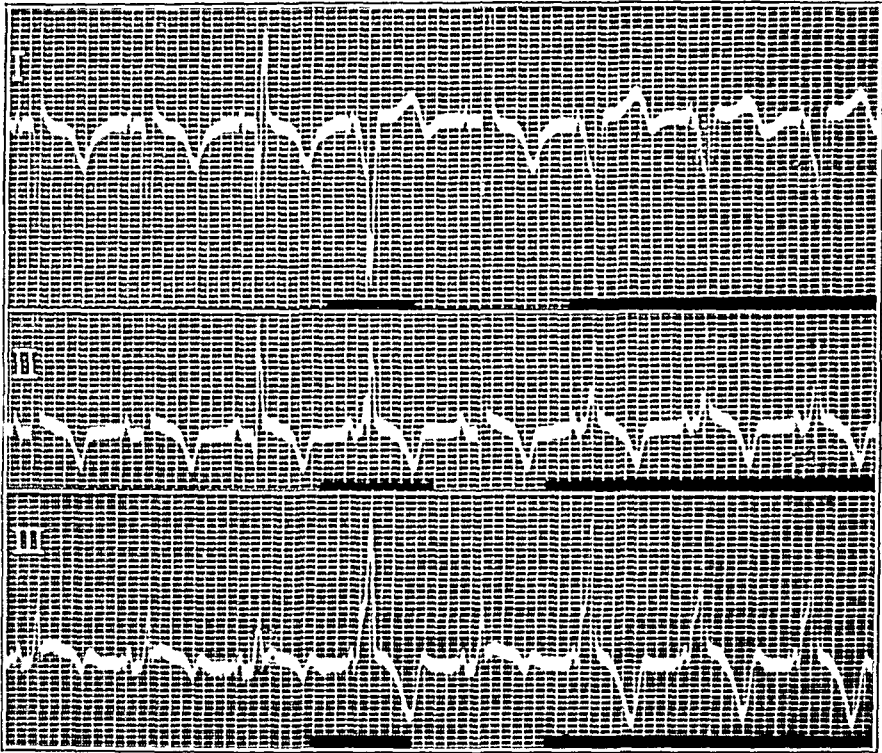


Fig. 6 (dog 1).—Standard leads showing normal complexes and complexes with a short PR interval and a wide QRS group. The black base line indicates the time the amplifier was turned on. For purposes of illustration a few of the QRS complexes have been retouched.

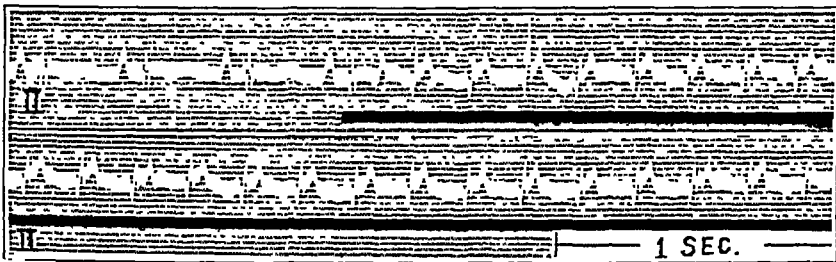


Fig. 7 (cat 13).—A continuous tracing of lead II, showing the tachycardia produced by retrograde stimulation of the auricle by the amplified QRS current. The time the amplifier was turned on is indicated by the black base line.

impulse originating in the sinus pacemaker to travel to the ventricles. Thus, one ventricle was stimulated and made to contract earlier than it would normally have done.

Figure 4 illustrates the results obtained for a cat heart. The input electrodes were placed on the left auricle, and the output electrodes were placed on the left ventricle. The electrocardiogram was recorded from the conventional limb leads. The auricular contractions remained perfectly constant, but by turning the amplifier on and off, abnormal complexes of the short PR-wide QRS type could be produced at will. The length of the PR interval could be regulated by taking the input of the amplifier from the right or left auricle—being shortest when the electrodes were placed in the region of the sinus node on the right auricle. With the output electrodes on the left ventricle a wide QRS complex with a right axis deviation was produced, while a left axis deviation resulted from stimulating the right ventricle (fig. 5).

Entirely similar results were obtained for the dog heart (fig. 6).

One other important point which must be considered is the paroxysmal tachycardia which so often is an accompanying feature. Figure 7 illustrates the tachycardia produced by reversing the flow of current in the abnormal conduction pathway. The ventricular QRS current was picked up by silver electrodes, amplified and returned to the auricle to produce a reentry phenomenon. In the illustration four normal beats are present. At this point the amplifier was turned on, and there follow a premature auricular beat and a tachycardia of supraventricular origin at a rate of 300 per minute—about double the normal rate. This has the appearance of a nodal rhythm but may be auricular in origin.

#### COMMENT

This syndrome has been generally described in the literature under the title "bundle branch block with a short PR interval," but it seems to us that the descriptive term short PR interval and a prolonged QRS complex, used by Wolferth and Wood,<sup>10</sup> is preferable. Whereas the term bundle branch block usually denotes some degree of cardiac damage, patients with this syndrome are almost invariably free of evidence of cardiac disease unless they are in the age group in which arteriosclerosis is frequent.

The concept of ventricular asynchronism with premature stimulation of one ventricle was first introduced by Wolferth and Wood<sup>10</sup> in this country and by Holzmänn and Scherf<sup>11</sup> in Europe. Wolferth and Wood

10. Wolferth, C. C., and Wood, F. C.: The Mechanism of Production of Short P-R Intervals and Prolonged QRS Complexes in Patients with Presumably Undamaged Hearts: Hypothesis of an Accessory Pathway of A-V Conduction (Bundle of Kent), *Am. Heart J.* 8:297 (Feb.) 1933.

11. Holzmänn, M., and Scherf, D.: Ueber Elektrokardiogramme mit verkürzter Vorhof-Kammer-Distanz und positiven P-Zacken, *Ztschr. f. klin. Med.* 121:404, 1932.

expressed the opinion that the premature stimulation of one ventricle was due to an abnormal conducting system between the auricle and ventricle, such as the bundle described by Kent<sup>12</sup> in 1892. These authors explained the paroxysmal tachycardia by assuming a retrograde conduction over a bundle of Kent, or some similar structure, causing a reentry phenomenon in the auricles with the production of a tachycardia.

Recently Glomset and Glomset<sup>13</sup> described connections between the auricles and ventricles in mammalian and human hearts and concluded that tissue structures bridging the auriculoventricular groove may often be present. This lends further credence to the concept of an abnormal conducting system in this syndrome. Thus far, no human heart exhibiting this syndrome has been completely studied<sup>14</sup> at autopsy, and final decision as to the underlying anatomic relations must await such an event. An abnormal pathway around the auriculoventricular node or a "longitudinal dissociation of the node"<sup>15</sup> could theoretically cause the syndrome and would probably be difficult to demonstrate anatomically. Such a path might be supposed to be under vagal control, which would explain the disappearance of the short PR interval and prolonged QRS complex following the administration of atropine or exercise.

Other points noted in cases of the syndrome in human beings are (1) the tendency for the PT interval (the time from the beginning of the P wave to the end of the QRS complex) to remain constant in normal and abnormal complexes in the same person and (2) the slurring of the initial deflection in the wide QRS groups. The PT interval may be constant in the wide QRS complexes produced in animals, but it depends mainly on where the electrodes are placed on the heart. When the input and output electrodes are both near the auriculoventricular groove this relation usually holds. Some degree of slurring of the initial deflection, particularly in dog hearts, was also apparent.

The finding of auricular premature contraction with little change in the QRS complexes in our cases of the syndrome in human beings seems to us to be another point in favor of an abnormal pathway and against the hypothesis of a double rhythm with two interfering pacemakers, as suggested by Hunter, Papp and Parkinson.<sup>6</sup> Wolferth<sup>8</sup> has

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12. Kent, A. F. S.: Observations on the Auriculo-Ventricular Junction of Mammalian Hearts, *Quart. J. Exper. Physiol.* **7**:193, 1914.

13. Glomset, D. J., and Glomset, A. T. A.: A Morphologic Study of the Cardiac Conduction System in Ungulates, Dog, and Man, *Am. Heart J.* **20**:389 (Oct.) 1940.

14. Ohnell, R. F.: Postmortem Examination and Clinical Report of a Case of the Short P-R Interval and Wide QRS Wave Syndrome (Wolff, Parkinson and White), *Cardiologia* **4**:249 (Aug.) 1940.

15. Scherf, D.: An Experimental Study of Reciprocating Rhythm, *Arch. Int. Med.* **67**:372 (Feb.) 1941.

also noted auricular extrasystoles in this type of electrocardiogram and has expressed the belief that the appearance of the ventricular complexes is in favor of an accessory conducting pathway.

By the use of a suitable time delay device the auricular current may be amplified, delayed and introduced at any point in succeeding cardiac cycles. Such an apparatus has been constructed and gives promise of aiding in further study of this and other problems of cardiac physiology.

#### SUMMARY AND CONCLUSIONS

The syndrome of short PR interval with a prolonged QRS complex is briefly reviewed, and 2 cases are reported.

An experimental study of cats and dogs showed that by the use of an abnormal electrical conducting pathway it was possible to produce electrocardiographic patterns closely resembling those occurring in human beings with the syndrome.

We feel the most logical explanation of this syndrome at present is a ventricular asynchronism, with premature contraction of one ventricle activated by an abnormal conducting pathway.

Further study, with a modification of the apparatus used, may be helpful in elucidating other problems in cardiac physiology.

NOTE.—The following interesting articles have appeared since this paper was submitted for publication: Levine, S. A., and Beeson, P. B.: The Wolff-Parkinson-White Syndrome, with Paroxysms of Ventricular Tachycardia, *Am. Heart J.* 22: 401 (Sept.) 1941, and Wolferth, C. C., and Wood, F. C.: Further Observations on the Mechanism of the Production of a Short P-R Interval in Association with Prolongation of the QRS Complexes, *ibid.* 22: 450 (Oct.) 1941.

# RELATION BETWEEN THE SYMPTOMS OF UREMIA AND THE BLOOD LEVELS OF THE PHENOLS

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Among the metabolites which are retained in the body during renal insufficiency, the phenols have received relatively little attention. The fact that these compounds have practical significance because of their correlation with the depressive symptoms of uremia is confirmed by these studies at the Long Island College Hospital, Brooklyn. It is recognized, of course, that the phenols are only one of the various factors contributing to the symptoms noted in uremia.

The phenols are compounds characterized by the presence of a free hydroxyl group and are divided into free and conjugated forms. The free phenols include both volatile and nonvolatile acids. Orthocresol and paracresol are examples of the free volatile phenols and parahydroxybenzoic acid of the free nonvolatile group. A conjugated phenol consists of a free phenol in combination with sulfuric or glycuronic acid.

Attention was first drawn to the significance of the phenol bodies by Becher,<sup>1</sup> who noted that the symptoms of chronic phenol intoxication were similar to the symptoms of uremia. He pointed out that an increase in the blood phenols more closely paralleled the development of the symptoms of uremia than did the increase of any other of the blood constituents. It was his contention that of the entire group of the blood phenols the level of the free phenols had the greatest significance and more closely paralleled the uremic symptoms. Since Becher's work, Marcolongo<sup>2</sup> has verified the fact that as the degree of uremia increases, the blood level of the phenols increases.

Marcolongo expressed agreement with Becher that the level of the free phenols was more significant than was the level either of the total phenols or of the conjugated phenols. No distinction was made between the symptoms of excitation and those of depression until the publication

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From the Department of Medicine of the Long Island College of Medicine.

1. Becher, E.: Studien über die Pathogenese der echten Urämie, Zentralbl. f. inn. Med. **46**:369 (April 25) 1925; Pathogenese, Symptomatologie und Therapie der Urämie, *Ergebn. d. ges. Med.* **18**:51, 1933.

2. Marcolongo, F.: Ricerche cliniche e sperimentali sui fenoli nell'uremia; alterazioni dei fenoli del sangue (volatili, non volatili ed eteroinsolubili) nell'uremia e loro relazione con i fenomeni clinici, *Riv. di pat. sper.* **8**:450-490, 1937.

of Mason and associates<sup>3</sup> appeared in 1937. These workers noted weakness, apathy and ataxia in dogs given intravenous doses of phenol or a related substance and correlated the symptoms of depression with the phenol levels. However, no information was given on the relation of the blood levels of the phenols and the symptoms of depression in uremia as encountered in man.

#### MATERIAL AND METHODS

These studies were carried out on 51 patients in the wards of the Long Island College Hospital. Twenty-eight of these patients had some form of renal disease, and of these 28, 23 were uremic. The remainder of the patients were chosen at random and had no evidence of nitrogen retention or of renal disease. The latter group was used for the determination of average normal phenol values.

Clinical evaluation of the degree of depression was made whenever blood was collected for analysis. The severity of depression was graded from absence of symptoms through the intermediate stages of retardation, drowsiness and semicoma to complete coma. A patient was considered as retarded when his reaction time to questions was noticeably slow and there was no desire to be up and about. A drowsy patient was one who was sleepy and inclined to doze most of the time. Semicoma was that degree of depression in which the patient was stuporous but could still be roused. Coma was that state of depression from which a patient could no longer be roused. In addition to the phenols, urea nitrogen, alkali reserve, calcium and phosphorus were also measured.

The level of the phenols in the blood was determined by the method of Theis and Benedict, as described by Peters and Van Slyke in "Quantitative Clinical Chemistry."<sup>4</sup>

#### RESULTS

Twenty-five determinations of the free and the conjugated phenols were made on 23 of the patients who had no evidence of renal disease or of nitrogen retention. The average blood levels obtained were 1.67 mg. per hundred cubic centimeters for the total phenols, 1.41 mg. for the free phenols and 0.21 mg. for the conjugated phenols. The range of variation was 1.25 to 1.98 mg. for the total phenols, 1.00 to 1.77 mg. for the free phenols and 0.08 to 0.47 mg. for the conjugated phenols. Peters and Van Slyke recorded 1.70 mg. per hundred cubic centimeters as the normal level of the total phenols in the blood plasma.

A total of 70 analyses for the phenols was made for 28 patients with renal disease, 23 of whom were uremic (urea nitrogen exceeding 50 mg. per hundred cubic centimeters of blood). The results obtained, together with the corresponding degrees of depression, are recorded in tables 1, 2 and 3.

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3. Mason, M. F.; Resnik, H.; Minot, A. S.; Rainey, J.; Pilcher, C., and Harrison, T.: Mechanism of Experimental Uremia, *Arch. Int. Med.* **60**:312 (Aug.) 1937.

4. Peters, J. P., and Van Slyke, D. D.: *Quantitative Clinical Chemistry*, Baltimore, Williams & Wilkins Company, 1932, vol. 2, p. 658.

It will be noted in table 1 that, in general, the higher the total blood phenol level, the more marked the patient's depression. There were several determinations, denoted by a double dagger or a section symbol,

TABLE 1.—*Levels of Total Phenols in the Blood of Twenty-Eight Patients with Renal Disease*

Total Phenols, Mg./100 Co. *	Degree of Depression †	Total Phenols, Mg./100 Cc. *	Degree of Depression †
6.09.....	5	2.50	1
5.50.....	5	2.45	1
5.24.....	4	2.40	2
4.90.....	3	2.29	2
4.85.....	3	2.29	2
4.70 ‡.....	1	2.26	1
4.68 ‡.....	1	2.24	2
4.56.....	4	2.22	2
4.30.....	5	2.21 ‡	1
4.05.....	4	2.20	1
4.04.....	1	2.15	2
3.97 §.....	1	2.15	1
3.90.....	3	2.13	1
3.89.....	4	2.12	1
3.77.....	4	2.11	1
3.68.....	4	2.11	1
3.65.....	4	2.10	2
3.64.....	4	2.10	1
3.61.....	4	2.09	1
3.60 §.....	1	2.04	3
3.59 §.....	1	2.02	1
3.57.....	4	2.00	1
3.38.....	4	2.00	1
3.30.....	3	1.98	1
3.30 §.....	1	1.98	1
3.23.....	3	1.96	1
3.15.....	3	1.95	1
3.00.....	4	1.92	1
2.90.....	1	1.88 §	1
2.89.....	2	1.83	1
2.75.....	1	1.80	1
2.70.....	2	1.78	1
2.70.....	1	1.65	1
2.55.....	1	1.51	1
2.55.....	1	1.40	1

\* The readings denoted by a double dagger were serial determinations made on 1 patient. The readings denoted by a section symbol were determinations made on a second patient. Neither of these patients showed evidence of depression, although their blood phenol levels were high.

† The figures bear the following significance: 1, absence of symptoms; 2, retardation; 3, drowsiness; 4, semicoma, and 5, coma.

‡ This patient had a phosphorus level of 8.3 mg. per hundred cubic centimeters when the blood phenol level was 4.68 mg. Mason has stated that the phosphorus and phenols have an antagonistic action.

§ This patient had a spinal fluid level of 0.89 mg. per hundred cubic centimeters for the total phenols when his blood level for the total phenols was 3.97 mg. The normal level for total phenols in the spinal fluid is 0.7 mg. A spinal fluid level of 3.00 mg. has been obtained on a comatose patient, with a blood level of 3.03 mg. for the total phenols.

in which the phenol level was high but the patient showed little evidence of depression. These represent determinations made on the blood of 2 patients and account for most of the discrepancies in correlation.

Table 2 illustrates the relation of the free phenols to the depressive symptoms of uremia, and table 3, the relation of the conjugated phenols

to the degree of depression. The corresponding correlation graphs (figs. 1, 2 and 3) also illustrate these relations.

It is evident that the determinations of the total phenols correlated more closely with the degree of depression in renal insufficiency than did determinations of the free or conjugated phenols. In this respect, the findings conflict with those of Becher and of Marcolongo, who con-

TABLE 2.—*Levels of Free Phenols in the Blood of Twenty-Eight Patients with Renal Disease*

Free Phenols, Mg./100 Cc. *	Degree of Depression †	Free Phenols, Mg./100 Cc.*	Degree of Depression †
5.00.....	5	1.87	1
4.71.....	3	1.85	1
4.00.....	5	1.82	2
4.00.....	4	1.80	3
3.95.....	5	1.80	1
3.75.....	1	1.78	2
3.70.....	4	1.75	2
3.70.....	4	1.70	1
3.12.....	4	1.70	1
3.05 †.....	1	1.70	2
3.04 §.....	1	1.70	2
3.03.....	3	1.68	1
3.00 §.....	1	1.60	2
3.00.....	3	1.60	1
2.90.....	4	1.60 §	1
2.90.....	3	1.51	1
2.90 §.....	1	1.50	5
2.88.....	4	1.47	1
2.85.....	4	1.45	1
2.85 §.....	1	1.41 §	1
2.80.....	1	1.40	1
2.76 §.....	1	1.40	1
2.71.....	4	1.40	1
2.70.....	4	1.35	1
2.58.....	4	1.30	1
2.50.....	4	1.25	1
2.40.....	2	1.25	1
2.16.....	3	1.25	1
2.08.....	1	1.23	2
2.02.....	4	1.22	1
2.01.....	1	1.21	1
2.00.....	2	1.15	1
1.98.....	1	1.15	1
1.95.....	1	1.10	1
1.90.....	1		

For the meaning of the symbols see table 1.

cluded that the free phenols were most important and were more closely correlated with the symptoms of renal insufficiency.

In the acidosis of renal insufficiency a complete accounting of all the acid radicals has not been made. The total degree of acidosis is often more than can be accounted for by known acid radicals, and many attempts have been made to identify the unknown compounds. It was suggested by Becher that these heretofore unidentified blood constituents



were ether-soluble organic acids. As the free phenols are included in the ether-soluble acidic free organic substances, a comparison was made between the alkali reserve and the free phenols.

In table 4 the blood level of the free phenols has been set against the carbon dioxide content of the blood. It can be seen that there was no significant correlation present and that the levels of the two blood con-

TABLE 3.—*Levels of Conjugated Phenols in the Blood of Twenty-Eight Patients with Renal Disease*

Conjugated Phenols, Mg./100 Cc. *	Degree of Depression †	Conjugated Phenols, Mg./100 Cc. *	Degree of Depression †
4.00.....	5	0.55 §	1
1.98.....	4	0.54 §	1
1.83 †.....	1	0.54	1
1.66.....	2	0.51	2
1.65 †.....	1	0.49	2
1.31.....	4	0.48	1
1.30.....	1	0.45	2
1.24.....	4	0.45	4
1.15.....	1	0.40	1
1.15.....	1	0.40	2
1.15.....	1	0.40	2
1.11.....	1	0.36	1
1.09.....	5	0.35	4
1.07.....	3	0.35	5
1.01.....	1	0.32	1
1.00.....	3	0.30	3
0.97 §.....	1	0.29	1
0.95.....	4	0.29	1
0.95.....	1	0.28 §	1
0.92.....	4	0.28	1
0.90.....	4	0.27	1
0.90.....	5	0.26	1
0.88.....	4	0.26	1
0.86.....	4	0.25	1
0.80.....	4	0.24	1
0.80 §.....	1	0.18	1
0.80.....	1	0.18	1
0.78.....	1	0.17	1
0.74.....	4	0.14	3
0.73.....	1	0.13	1
0.72.....	1	0.12	1
0.70.....	2	0.12	1
0.70 §.....	1	0.10	1
0.69.....	2	0.00	2
0.62.....	1		

For the meaning of the symbols see table 1.

stituents varied independently. This is further illustrated by the corresponding correlation graph (fig. 4).

Eighteen of the 28 patients with renal disease died, and 10 showed clinical improvement. Of those who died, 8 had serious complicating diseases, such as Boeck's sarcoid, mesenteric thrombosis or carcinoma. The average total phenol value of the terminal determination for the 10 patients who died without evidence of serious complicating disease was

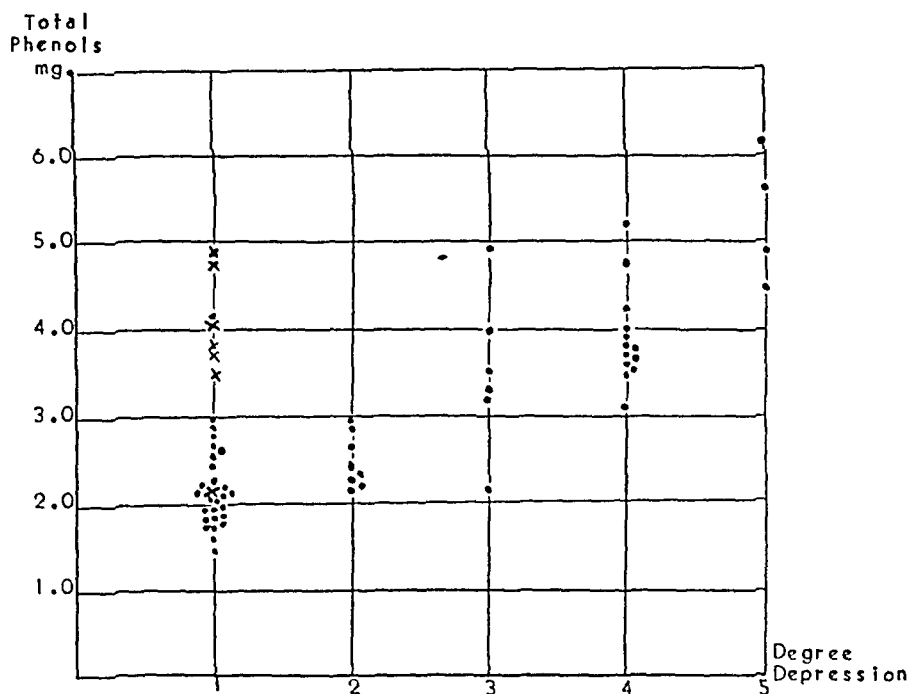


Fig. 1.—The correlation between the level of total phenols and the degree of depression noted in the patient.

In this chart and in the accompanying charts, the figures referring to the degree of depression bear the following significance: 1, absence of symptoms; 2, retardation; 3, drowsiness; 4, semicoma and 5, coma.

The determinations denoted by *X* here and in figures 2 and 3 are those for the 2 patients described in footnotes \*, ‡ and § of table 1. It is evident from a comparison of this figure with figures 2 and 3 that the total phenols show the greatest degree of correlation with the symptoms of depression. The conjugated phenols show the least degree of correlation.

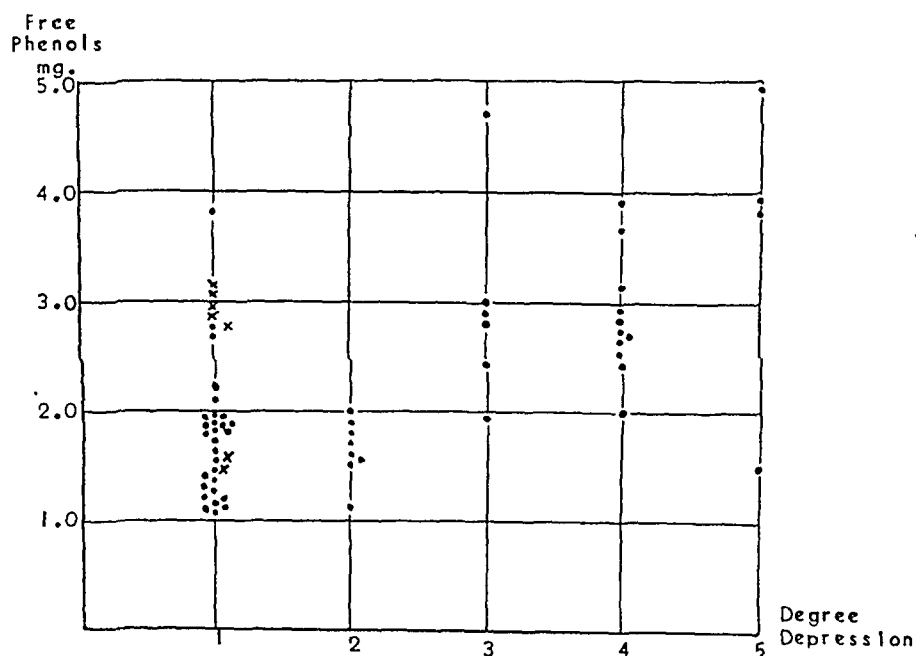


Fig. 2.—The correlation between the level of free phenols and the degree of depression.

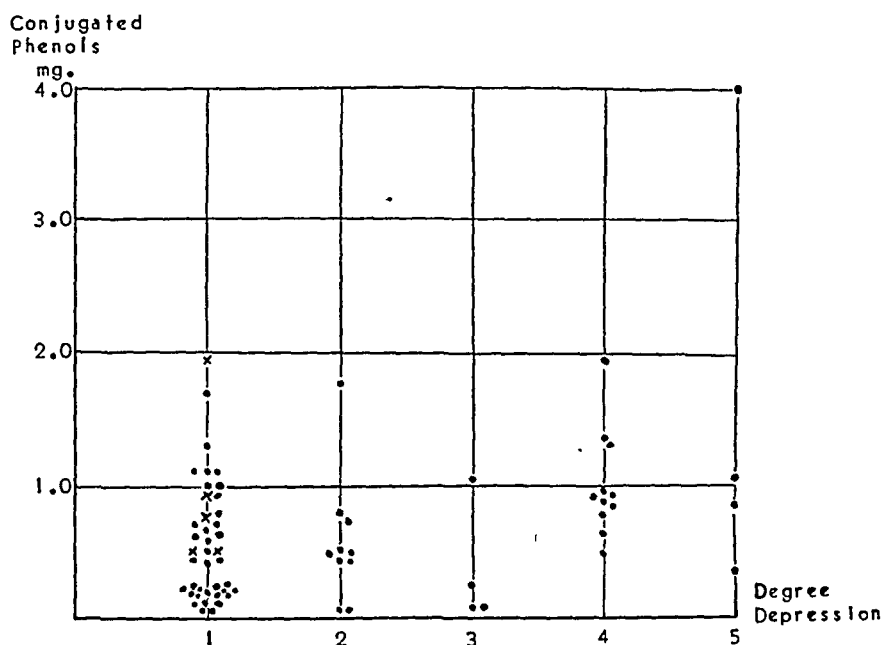


Fig. 3.—The correlation between the level of conjugated phenols and the degree of depression.

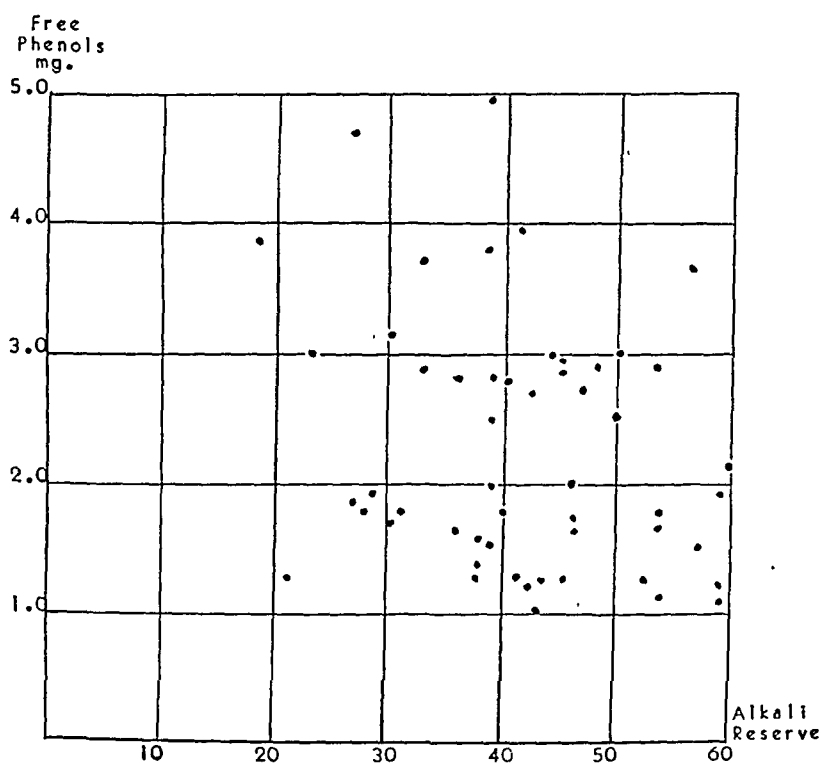


Fig. 4.—The lack of correlation between the free phenols and the alkali reserve (carbon dioxide, volumes per cent).

TABLE 4.—*Comparison of the Free Phenols and the Carbon Dioxide Content of the Blood of Twenty-Eight Patients with Renal Disease*

Free Phenols, Mg./100 Cc.	Alkali Reserve Carbon Dioxide, Volumes per Cent	Free Phenols, Mg./100 Cc.	Alkali Reserve, Carbon Dioxide, Volumes per Cent
5.00.....	38	1.89	59
4.71.....	27	1.90	27
4.00.....	41	1.87	54
3.95.....	18	1.85	46
3.75.....	38	1.82	31
3.70.....	33	1.80	40
3.70.....	56	1.78	28
3.20.....	30	1.75	30
3.05.....	50	1.70	46
3.04.....	44	1.70	36
3.04.....	23	1.70	54
3.00.....	45	1.60	38
2.90.....	45	1.60	39
2.90.....	53	1.51	57
2.90.....	48	1.47	38
2.88.....	33	1.45	38
2.85.....	36	1.41	41
2.85.....	39	1.40	53
2.80.....	40	1.40	21
2.76.....	47	1.35	45
2.70.....	42	1.30	43
2.58.....	50	1.25	59
2.50.....	39	1.25	42
2.16.....	60	1.25	59
2.08.....	46	1.15	54
2.02.....	39	1.15	59
2.00.....	29	1.10	43

TABLE 5.—*Comparison of the Levels of Total Phenols, Free Phenols and Conjugated Phenols in Twenty-Eight Patients with Renal Disease*

Total Phenols, Mg./100 Cc.	Free Phenols, Mg./100 Cc.	Conjugated Phenols, Mg./100 Cc.
Patients Who Showed Improvement		
3.90	2.90	1.01
2.90	2.80	1.00
2.40	2.40	0.80
2.21	1.90	0.32
2.11	1.60	0.27
2.02	1.51	0.26
1.92	1.41	0.25
1.78	1.40	0.12
1.65	1.25	0.10
1.51	1.10	0.00
Average 2.24	Average 1.82	Average 0.41
Patients Who Died		
6.09	5.00	1.65
4.90	4.00	1.31
4.70 *	3.95	1.09
4.30	3.12	0.92
3.89	3.05	
3.77	3.00	
3.64	2.99	0.74
3.57	2.85	0.70
3.30	2.58	0.45
2.70 †	2.00	0.35
		0.30
Average 4.08	Average 3.24	Average 0.84

\* This patient was discharged and was followed at home by a private physician. She died about one month after discharge.

† This patient left the hospital without consent. He died several months later.

4.08 mg. per hundred cubic centimeters. The average value for the free phenols was 3.24 mg. and for the conjugated phenols 0.84 mg.

The 10 patients who showed clinical improvement had an average total phenol value of 2.24 mg. per hundred cubic centimeters on the last blood analysis made before discharge from the hospital, and the average free phenol value was 1.82 mg. The average level of conjugated phenols was 0.41 mg. The marked difference in the terminal phenol levels of the patients who died and of those who improved indicated the serious prognostic import of high blood phenol levels. In this series, the highest phenol level noted for any patient who improved was 3.90 mg. per

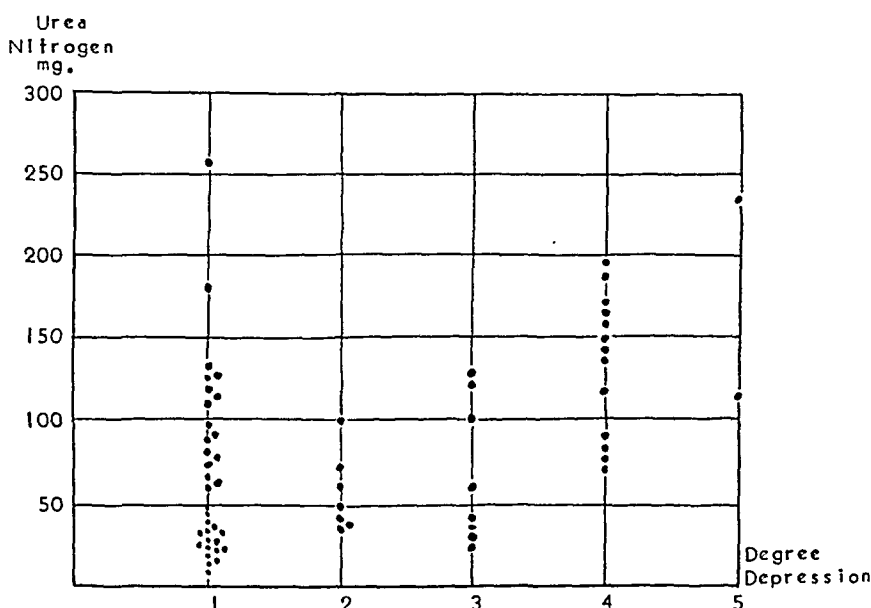


Fig. 5.—The degree of correlation between the symptoms of depression and the blood level of urea nitrogen is slight; that noted for the total phenols and the depressive phenomena is more marked (fig. 1).

hundred cubic centimeters for the total phenols, 2.90 mg. for the free phenols and 1.01 for the conjugated phenols (table 5).

In figure 5, the blood level of the urea nitrogen has been set against the degree of depression noted in the patient. A correlation was evident, but it was not as great as the correlation between the total phenols and the degree of depression.

#### SUMMARY AND CONCLUSIONS

1. In 21 of 23 uremic patients the degree of cerebral depression showed a direct correlation with the height of the blood level of the phenols.

2. The total phenols appeared to have a greater correlation with the degree of depression than did the free or the conjugated phenols.

3. The blood level of the total phenols showed better correlation with the degree of cerebral depression than did the blood urea nitrogen.

4. The suggestion that the free phenols may account for the unidentified acid radicals in renal acidosis was not supported. The blood level of the free phenols showed no correlation with the carbon dioxide content (degree of acidosis) of the blood.

5. High phenol levels in the blood proved to be of grave prognostic import in this series.

6. No patient recovered who had a blood level above 3.90 mg. per hundred cubic centimeters for the total phenols, 2.90 mg. for the free phenols or 1.01 mg. for the conjugated phenols.

# DIFFUSION OF SULFANILAMIDE INTO ARTIFICIAL PERITONEAL FLUID

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PHILADELPHIA

It is commonly believed that sulfanilamide compounds diffuse readily from the blood into the tissue fluids and that an equilibrium between these two mediums is established rapidly. In commenting on this phenomenon, the majority of authors refer to the observations of Marshall and Long,<sup>1</sup> which led to the conclusion that the distribution of sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) between the blood and the tissues is "complete or nearly complete in five to ten minutes" after its administration intravenously. This conclusion was based on the observation that the most marked decrease in the concentration of sulfapyridine in the blood occurred during the first five to ten minutes, with only a relatively slight drop during the next hour. Review of their data, however, reveals that few determinations were made five and ten minutes after the compound was administered and that in the majority of instances sulfapyridine was present in the blood (and presumably in the tissues and tissue fluids) prior to its intravenous injection, a fact which might have influenced the rate of its subsequent diffusion from the blood.

Marshall, Emerson and Cutting<sup>2</sup> determined the concentration of sulfanilamide in the blood and the cisternal fluid of dogs at intervals after oral administration. After one hour the concentration in the cisternal fluid (0.5 mg. per hundred cubic centimeters) was 12.5 per cent of that in the blood (4 mg. per hundred cubic centimeters), the ratio increasing to about 70 per cent in four hours. In a patient with peri-

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1. Marshall, E. K., Jr., and Long, P. H.: The Intravenous Use of Sodium Sulfapyridine, *J. A. M. A.* **112**:1671 (April 29) 1939.

2. Marshall, E. K., Jr.; Emerson, K., Jr., and Cutting, W. C.: Para-Aminobenzenesulfonamide: Absorption and Excretion; Method of Determination in Urine and Blood, *J. A. M. A.* **108**:953 (March 20) 1937.

cardial effusion, Nathanson<sup>3</sup> found the concentration of sulfapyridine in the pericardial fluid to be 1.9 mg. per hundred cubic centimeters one hour after intravenous injection of the sodium salt and 2.3 mg. after one and one-half hours, the level in the blood being 6 mg. per hundred cubic centimeters. Bellows and Chinn<sup>4</sup> found that the concentration of sulfanilamide in the aqueous humor of dogs one hour after oral administration was about 33 per cent of that in the blood, increasing to a maximum of about 61 per cent four hours after administration. According to Marshall, Emerson and Cutting,<sup>5</sup> four hours after oral administration of sulfanilamide the concentrations in the skeletal muscle, heart muscle, liver, lungs, spleen and skin were essentially the same as in the blood. The studies of Sadusk, Blake and Seymour<sup>6</sup> indicated a variable degree of diffusion of sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) into pleural and peritoneal effusions four hours after its administration to patients with congestive heart failure, tuberculous pleurisy and cirrhosis of the liver.

It appears that the widespread belief in the rapidity of diffusion of sulfanilamide compounds, particularly sulfanilamide itself, rests on rather meager factual evidence. This investigation was designed to study the rate of passage of sulfanilamide from the blood into fluid introduced into the peritoneum.

#### MATERIAL AND METHODS

Observations were made on 3 dogs, weighing 13 to 15 Kg., and 10 rabbits, weighing 1.5 to 3 Kg. A 0.9 per cent solution of sodium chloride was introduced into the peritoneum, the dogs receiving 100 cc. per kilogram and the rabbits 250 cc. per kilogram. A 0.5 per cent solution of sulfanilamide was slowly injected intravenously, each animal receiving 150 mg. per kilogram. No untoward symptoms were observed. Samples of blood (from the femoral artery in the dogs and from the heart in the rabbits) and of peritoneal fluid were obtained at intervals of five minutes to seven hours after completion of the injection, and the sulfanilamide content was determined by the method of Bratton and Marshall,<sup>7</sup> using the Evelyn photoelectric colorimeter. The blood was oxalated and centrifuged, and the determinations were made on the plasma. The abdomen was manipulated, and fluid was repeatedly withdrawn and reinjected immediately before securing each sample to insure uniform composition of the fluid.

3. Nathanson, M. H.: Diffusion of Sulfonamide Compounds into the Human Pericardium, *J. A. M. A.* **116**:280 (Jan. 25) 1941.

4. Bellows, J., and Chinn, H.: The Distribution of Sulfanilamide in the Eye, *J. A. M. A.* **112**:2023 (May 20) 1939.

5. Marshall, E. K., Jr.; Emerson, K., Jr., and Cutting, W. C.: Distribution of Sulfanilamide in the Organism, *J. Pharmacol. & Exper. Therap.* **61**:196 (Oct.) 1937.

6. Sadusk, J. F., Jr.; Blake, F. G., and Seymour, A.: Observations on the Absorption, Excretion, Diffusion, and Acetylation of Sulfathiazole in Man, *Yale J. Biol. & Med.* **12**:681 (July) 1940.

7. Bratton, A. C., and Marshall, E. K., Jr.: A New Coupling Component for Sulfanilamide Determination, *J. Biol. Chem.* **128**:537 (May) 1939.



*Distribution of Sulfanilamide (Milligrams per Hundred Cubic Centimeters) Between Blood Plasma and Artificial Peritoneal Fluid Following Intravenous Injection*

Animal	Form of Sulfanilamide	Body Fluid*	Elapsed Time Between Injection and Withdrawal of Samples of Body Fluid									
			Minutes			Hours						
			5	15	30	1	2	3	4	5	6	7
Dog 1.....	.....	P	6.6	...	...	4.2	...	3.3	...	2.5	...	...
		F	0.4	1.1	...	3.0	3.7	3.6	3.5	3.1	...	...
Dog 2.....	.....	P	7.2	...	...	4.8	...	4.0	...	3.0	...	...
		F	0.5	...	1.8	3.1	4.6	4.4	4.2	3.7	...	...
Dog 3.....	.....	P	6.8	...	...	3.9	...	3.4	...	2.8	...	...
		F	0.2	...	1.2	3.2	3.8	3.8	3.7	3.4	...	...
Rabbit 1	Acetylated	P	...	...	...	...	0.1	...	0.1	...	...	...
		F	...	0.0	0.0	0.2	0.2	0.2	0.2	...	...	...
	Free	P	...	...	8.5	...	6.8	...	5.2	...	...	...
		F	...	1.4	2.2	4.9	5.8	4.0	3.8	...	...	...
Rabbit 2	Acetylated	P	...	...	...	...	...	3.9	...	...	...	...
		F	...	...	...	...	...	2.5	2.9	2.4	...	...
	Free	P	...	...	...	...	...	3.6	...	...	...	...
		F	...	...	...	...	...	3.1	3.2	2.9	...	...
Rabbit 3	Acetylated	P	...	...	...	...	...	3.0	...	1.8	...	1.0
		F	...	...	...	...	...	1.0	0.9	0.8	0.9	...
	Free	P	...	...	...	...	...	0.8	...	0.3	...	0.0
		F	...	...	...	...	...	1.0	0.8	0.3	0.0	...
Rabbit 4	Acetylated	P	...	...	...	...	0.4	...	0.2	...	0.1	...
		F	...	...	...	...	0.0	0.1	0.1	0.1	0.2	0.1
	Free	P	...	...	...	...	6.8	...	4.4	...	3.1	...
		F	...	...	...	...	5.1	4.6	4.2	3.8	3.4	3.1
Rabbit 5	Acetylated	P	...	...	...	...	1.2	...	1.1	...	1.1	...
		F	...	...	...	...	0.5	0.4	0.4	0.4	0.5	0.5
	Free	P	...	...	...	...	6.0	...	4.9	...	3.4	...
		F	...	...	...	...	3.4	4.2	4.7	4.2	3.7	3.3
Rabbit 6	Acetylated	P	...	...	...	...	5.0	...	5.2	...	3.0	...
		F	...	...	...	...	2.1	1.2	3.2	3.3	2.9	...
	Free	P	...	...	...	...	2.8	...	1.1	...	0.6	...
		F	...	...	...	...	3.0	2.0	1.7	1.0	0.8	...
Rabbit 7	Acetylated	P	...	...	...	...	4.5	...	4.7	...	4.5	...
		F	...	...	...	...	0.3	1.8	1.9	2.4	2.3	...
	Free	P	...	...	...	...	3.7	...	2.8	...	1.6	...
		F	...	...	...	...	3.0	3.1	2.8	2.5	2.0	...
Rabbit 8	Acetylated	P	...	...	...	...	3.9	...	4.3	...	...	...
		F	...	...	...	...	1.1	3.1	2.9	...	...	...
	Free	P	...	...	...	...	3.3	...	2.3	...	...	...
		F	...	...	...	...	2.8	3.2	2.0	...	...	...
Rabbit 9	Acetylated	P	...	...	...	...	3.5	...	3.1	...	1.5	...
		F	...	...	...	...	0.6	0.6	1.4	1.5	1.2	...
	Free	P	...	...	...	...	3.5	...	1.5	...	0.6	...
		F	...	...	...	...	2.5	2.4	2.0	1.0	0.7	...
Rabbit 10	Acetylated	P	...	...	...	...	...	...	1.8	...	1.3	...
		F	...	...	...	...	1.4	...	2.2	...	1.8	...
	Free	P	...	...	...	...	...	...	0.9	...	0.2	...
		F	...	...	...	...	2.4	...	1.0	...	0.7	...

\* P, plasma; F, peritoneal fluid.

## RESULTS AND COMMENT

The data are presented in detail in the table. Inasmuch as it became apparent that equilibrium between the sulfanilamide in the blood and that in the peritoneal fluid was not established during the first hour, withdrawal of specimens was begun at the end of two hours for 7 of the 10 rabbits and at the end of three hours for 2 of them. Free sulfanilamide was present in the peritoneal fluid five minutes after its administration, but equilibrium between the fluid and the blood plasma was not attained for two to four hours. This equilibrium was roughly maintained during the subsequent fall in concentration of sulfanilamide in the plasma and in the peritoneal fluid, the concentration in the latter being usually slightly higher than that in the former during this period. As has been reported by other observers, there was considerable variation in the rate and the degree of acetylation. The acetylated fraction, except in a few instances in which its concentration was low, did not attain equilibrium between the plasma and the fluid before the sixth hour after the injection of the sulfanilamide.

If the artificial peritoneal fluid may be regarded as representative of the natural tissue fluids, these data suggest that sulfanilamide is not distributed throughout the body fluids as rapidly as is generally assumed.

# DIAGNOSIS OF ADDISON'S DISEASE

## FURTHER EXPERIENCE WITH THE CUTLER-POWER-WILDER SODIUM CHLORIDE RESTRICTION TEST

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In cases of typical Addison's disease the diagnosis is usually not difficult, but periodically cases are encountered in which the clinician desires all possible help in establishing or excluding this possibility. To this end a laboratory procedure was proposed in 1938 by Cutler, Power and Wilder.<sup>1</sup> They showed that when patients who had Addison's disease were placed on a specified diet and intake of fluids they excreted consistently higher concentrations of sodium and chloride in the urine than did patients following the same regimen who did not have Addison's disease. These authors stated: "The . . . procedure suggested requires fewer days for completion, subjects the patient to less risk of collapse, and in most cases is quite as informative as the six day period of restricted intake of salt heretofore resorted to for diagnostic purposes." The present paper deals with the results obtained in the application of this procedure during the two year period following the original publications.

### PROCEDURE

On the day preceding the first day of the test the patients received a general diet, without extra sodium chloride or adrenal cortical extract. If patients had

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This study was carried out in the metabolic service of Drs. R. M. Wilder, E. J. Kepler and E. H. Rynearson.

From the Division of Biochemistry, the Mayo Foundation (Dr. Power), and the Division of Medicine, the Mayo Clinic (Dr. Wilder).

1. Cutler, H. H.; Power, M. H., and Wilder, R. M.: Concentrations of Sodium, Chloride and Potassium in the Blood Plasma and Urine of Patients with Addison's Disease: Their Diagnostic Significance, Proc. Staff Meet., Mayo Clin. **13**:244-249 (April 20) 1938; Concentrations of Chloride, Sodium and Potassium in Urine and Blood: Their Diagnostic Significance in Adrenal Insufficiency, J. A. M. A. **111**:117-122 (July 9) 1938.

been receiving desoxycorticosterone acetate, the use of this substance was discontinued at least forty-eight hours prior to the test in the examination of all except 3 of the patients who had Addison's disease.

On the first day of the examination and daily thereafter until its completion, a standard weighed diet (table 1) was served which, by calculation, provided 0.95 Gm. of chloride, 0.59 Gm. of sodium and 4.1 Gm. of potassium. The fluid intake was not measured on the first day, but the free drinking of water was encouraged. On the afternoon of the first day 33 mg. of potassium per kilogram of body weight (15 mg. per pound) was administered in the form of potassium citrate dissolved in a glass of water (1 Gm. of potassium citrate provides 362 mg. of potassium).

On the second day the intake of fluid was maintained at 40 cc. per kilogram of body weight distributed over the waking hours. The same dose of potassium

TABLE 1.—*Diet Employed in the Standardized Diagnostic Procedure\**

	Breakfast	Dinner	Supper	Potassium	Sodium	Chloride
Vegetables						
Canned tomatoes.....	...	90	...	0.27	0.01	0.034
Lettuce.....	...	10	10	0.06	0.005	0.015
Canned peas.....	...	...	100	0.125	0.013	0.024
Baked potato.....	...	100	100	1.000	0.042	0.076
Fruit						
Peaches.....	...	100	...	0.125	0.022	0.004
Oranges.....	100	...	...	0.2	0.012	0.006
Grapefruit.....	...	...	100	0.2	0.004	0.005
Bananas.....	...	...	100	0.400	0.034	0.125
Bread, salt free.....	50	30	30	0.110	0.073	0.127
Jello.....	...	150	...	...	...	...
Butter, salt free.....	10	10	10	0.003	0.021	0.049
Cream, 20 per cent.....	25	25	75	0.158	0.044	0.1
Milk.....	...	...	200	0.3	0.102	0.212
Coffee, medium.....	300	200	...	0.5	...	...
Eggs.....	1	...	...	0.07	0.071	0.053
Beef, lean (weight before cooking)..	...	75	50	0.465	0.131	0.117
Jelly.....	20	20	20	0.076	0.008	0.002
Total.....				4.062	0.592	0.949

\* All quantities are measured in grams.

citrate that had been administered on the previous day was repeated on the morning of the second day.

On the third day 20 cc. of fluid per kilogram of body weight was administered before 11 a. m. Urine was collected between 8 a. m. and 12 noon on the third day. At 12 noon blood was drawn for analysis. The patient was weighed daily.

These studies have been conducted in the hospital in order that the patients might be under constant observation for the development of signs of impending crisis. In those instances in which crisis did develop blood was drawn for analysis and 1,000 cc. of a special solution was administered intravenously. This solution consisted of 5 per cent dextrose and 0.85 per cent sodium chloride to which had been added approximately 5 Gm. of sodium citrate (ampules of sterile sodium citrate utilized as an anticoagulant for blood transfusions are convenient) and 20 cc. of an active extract of the adrenal cortex.

## MATERIAL

The subjects of this report were 19 patients who had Addison's disease. For 11 of them the diagnosis had been made on clinical grounds alone; these were studied to obtain further confirmatory evidence of the efficacy of the procedure. For 5 the test was a necessary adjunct in establishing the proper diagnosis. For 3, observations were made during the administration of desoxycorticosterone acetate. In addition, 44 patients suffering from a variety of conditions, including many who had "functional" asthenia, were submitted to the test.

## RESULTS

*Response of Patients with Addison's Disease Who Were Not Receiving Desoxycorticosterone.*—Development of Crisis: Of the 16 patients having Addison's disease who were not receiving desoxycorticosterone, 10 (8 known to have and 2 suspected of having the disease) were unable to withstand the fifty-two hours of salt restriction. In these 10 patients symptoms of crisis developed sufficient in degree to permit the diagnosis of Addison's disease on clinical grounds.

The signs of impending crisis may be difficult to judge. Gastro-intestinal symptoms, such as abdominal fulness, discomfort and nausea, must be evaluated carefully before one concludes that they are significant. Such symptoms, which may be due to the irritant effects of the supplemental potassium citrate, were frequently present in cases of vague asthenia. The collapse that occurs in cases of Addison's disease is usually much more pronounced; restlessness may be prominent, vomiting tends to be severe, there may be considerable loss in weight, the blood pressure falls and the patient often refuses to eat or to leave his bed. Even superficial observation gives ample indication that the patient has become definitely ill. Needless to say, the facilities required for restorative treatment always should be instantly available.

The chemical data (table 2) obtained from the analysis of the blood drawn from these 10 patients at the time of discontinuation of the test were in general compatible with the impression of impending crisis. However, only occasionally did these values differ sufficiently from those obtained for the patients not having Addison's disease to be of diagnostic significance. Therefore, when patients for any reason are unable to complete the fifty-two hours of salt restriction, the clinician must be prepared to make his diagnosis on clinical grounds alone.

*Successful Completion of the Test:* Six patients who had Addison's disease and who were not receiving desoxycorticosterone acetate completed the fifty-two hour period of salt restriction. Five of them had a

concentration of chloride<sup>2</sup> in the final four hour specimen of urine which was more than 225 mg. per hundred cubic centimeters, while that of sodium was more than 165 mg., the levels originally proposed as characteristic of Addison's disease. A sixth patient, who had unequivocal signs and symptoms of Addison's disease and who became weak during restriction, responded with concentrations of sodium and chloride in the final specimen of urine which were not diagnostic. Examination of the composition of the plasma in this instance, however, revealed evidence of adrenal cortical insufficiency: The concentration of urea was 87 mg. per hundred cubic centimeters, the concentration of chloride was 302 mg. and that of sodium was 271 mg. (case 1, figs. 1 and 2).

TABLE 2.—*Composition of Blood\* Drawn from Patients with Addison's Disease at the Time of Discontinuance of the Salt Restriction Test Because of the Onset of Crisis*

Patients with Addison's Disease	Duration of Test Hr.	Sodium (in Plasma)	Chloride (in Plasma)	Potassium (in Plasma)	Urea Nitrogen (in Blood)
1.....	8½	274	290	....	28
2.....	10	294	330	21.2	
3.....	24	285	316	17.2	14
4.....	24	289	326	21.5	24
5.....	30	298	338	21.6	22
6.....	30½	306	330	25.6	10
7.....	33½	287	296	21.4	15
8.....	36	272	302	18.6	12
9.....	39	285	327	27.2	
10.....	48	295	313	21.0	9
Patients without Addison's disease.....	52				
Maximum.....		335	367	30.7	33
Average.....		310	343	19.8	16
Minimum.....		282	310	14.4	7

\* All constituents are measured in milligrams per hundred cubic centimeters.

Although the inadvisability of placing too much emphasis (so far as diagnosis is concerned) on the concentration of electrolytes in the blood has been stressed repeatedly, nevertheless, when extremely low values are encountered the possibility of Addison's disease must be considered seriously unless some other basis for this depletion can be found. This result may be compared with the observation made on a patient who did not have Addison's disease and in whose case the low concentration of chloride in the plasma was attributed to excessive vomiting. In this instance the concentration of sodium in the plasma was normal (case 2, figs. 1 and 2).

2. It is emphasized that the figure referred to represents only the chloride ion and is not to be confused with the commonly practiced method of reporting chlorides as sodium chloride.

When the concentrations of both chloride and sodium in the plasma and in the urine are compared diagrammatically (figs. 1 and 2), the points representing individual patients who have Addison's disease are found to be widely separated from the points representing the persons who were not suffering from adrenal cortical insufficiency.

*Response of Patients with Addison's Disease Who Were Receiving Desoxycorticosterone.*—Dryerre<sup>3</sup> and others have shown that if patients who have Addison's disease are subjected to salt restriction as here described while receiving desoxycorticosterone esters they respond

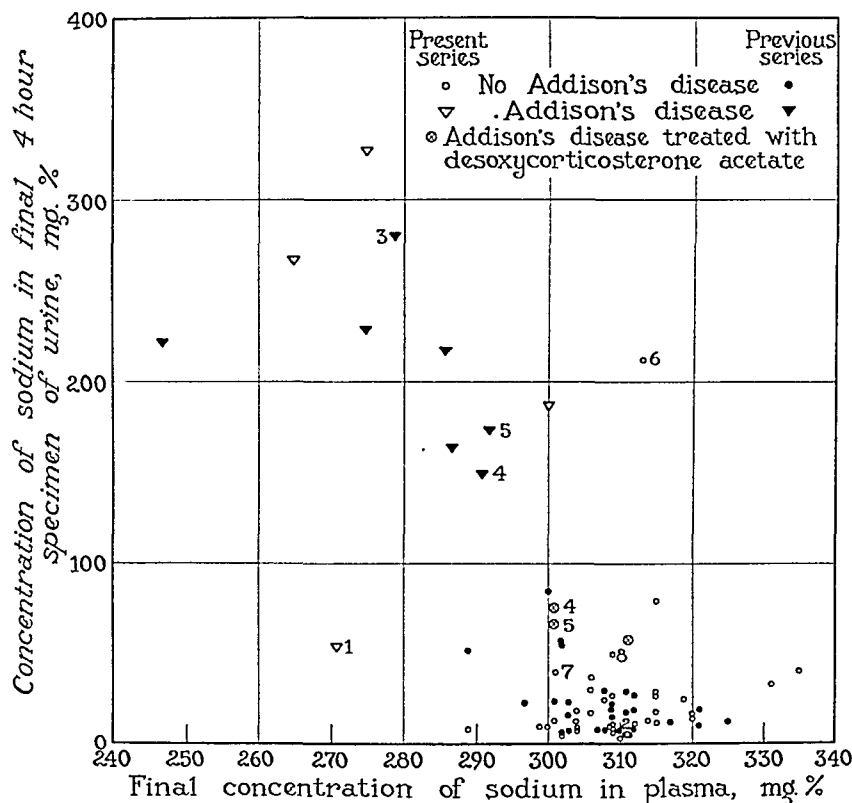


Fig. 1.—The relation between the concentration of sodium in the plasma and its concentration in the urine. The explanation of the numbered points is as follows: 1, the response of a patient with Addison's disease for whom the concentrations of sodium and chloride in the urine were within the normal range but for whom the concentrations of both sodium and chloride in the plasma were sufficiently low to be diagnostically significant; 2, the response of a subject not suffering from Addison's disease who had a low concentration of chloride in the plasma, which was attributed to excessive vomiting, and a normal concentration of sodium in the plasma; 3, the response of a patient with Addison's disease; 4 and 5, the response of patients before and during the administration of desoxycorticosterone acetate; 6, an apparently false positive response of a patient with carcinoma of the stomach, and 7 and 8, an illustration of the value of the concentration of sodium in the urine when the chloride response is equivocal.

3. Dryerre, H. W.: Effect of Desoxycorticosterone Acetate and Cortin on Salt Elimination in Addison's Disease, Brit. M. J. 1:971-973 (May 13) 1939.

much more like subjects not suffering from adrenal cortical insufficiency. Three of our patients who had Addison's disease and who were receiving this drug likewise responded in a manner which characterizes subjects who do not have Addison's disease. For 2 of them (cases 4 and 5,<sup>4</sup> figs. 1 and 2) the results obtained prior to treatment and during administration of desoxycorticosterone acetate may be compared.

*Response of Patients Not Suffering from Addison's Disease.*—The greatest value of the study of the response to salt restriction has been in helping to exclude the possibility of Addison's disease. Of 44

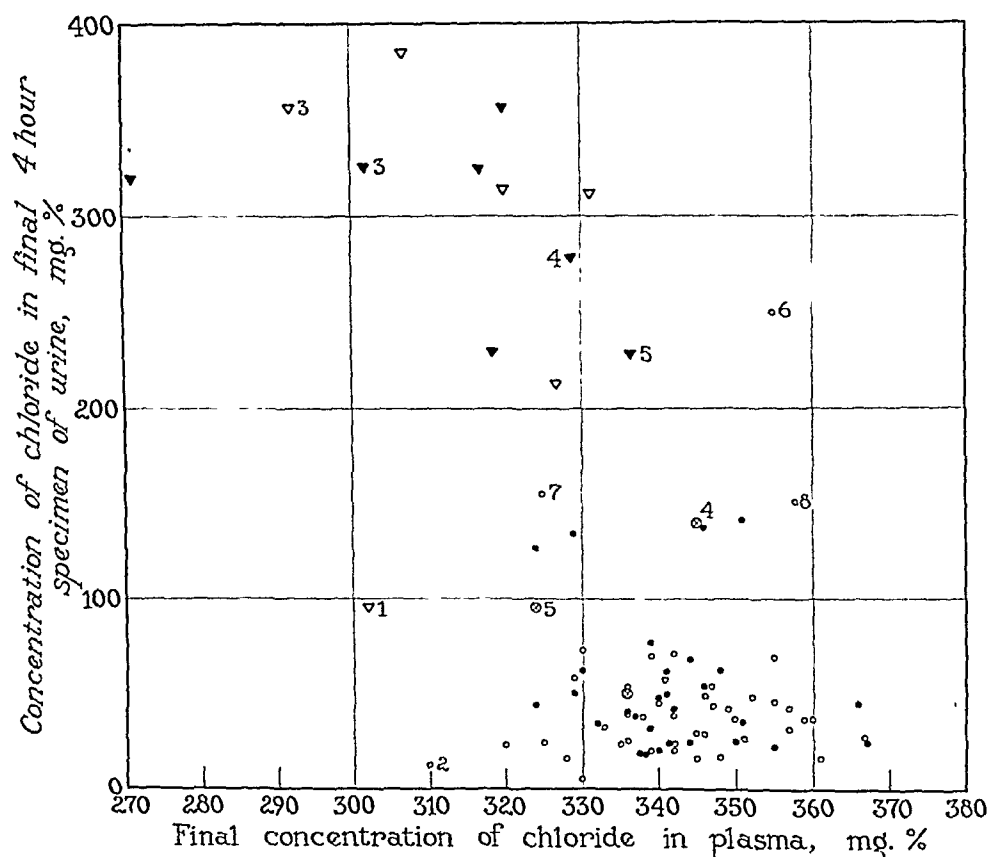


Fig. 2.—The relation between the concentration of chloride in the plasma and its concentration in the urine. The numbered points have the same significance as do those in figure 2 with the exception of 3, which represents the consistency of response of a patient with Addison's disease who was tested twice at a two year interval.

patients examined, 21 were placed finally in the class of patients suffering from vague asthenias variously termed nervous exhaustion, post-infectious exhaustion, vagotonia, neurocirculatory asthenia and anxiety state. Eleven patients had conditions certain manifestations of which

4. Tooke, T. B., Jr.; Power, M. H., and Kepler, E. J.: The Tolerance of Patients Suffering from Addison's Disease to Potassium While Such Patients Are Being Treated with Desoxycorticosterone Acetate, *Proc. Staff Meet., Mayo Clin.* 15:365-368 (June 5) 1940.



simulated some of the findings in Addison's disease: hyperthyroidism (2); tuberculous peritonitis (1); chronic glomerulonephritis (1); carcinoma of the lung, breast or stomach (3); sprue<sup>5</sup> (1); cirrhosis of the liver (1); functional anorexia and malnutrition (1), and vomiting of unknown origin (1). The remaining 12 had conditions which were distributed as follows: epilepsy (1); chronic infectious arthritis (1); duodenitis and duodenal ulcer (2); calculous cholecystitis (1); emphysema (1); schizophrenia or psychasthenia (2); Ménière's disease (1); diabetes mellitus (1); myasthenia gravis (1), and Cushing's syndrome (1).

With 1 exception all these patients responded to salt restriction and high intake of potassium essentially like normal persons: In other words, in the final four hour specimen of urine the concentration of chloride was less than 156 mg. per hundred cubic centimeters and that of sodium less than 85 mg. The data are shown graphically in figures 1 and 2. It will be seen that the points representing the subjects who did not have Addison's disease are localized in a small area distinctly separated from areas in which appear the points representing the subjects who had Addison's disease. An exception must be noted in the case of a patient who had gastric carcinoma (case 6, figs. 1 and 2). Although the concentration of electrolytes in the urine of this subject at the end of the period of salt restriction was similar to that characteristic of Addison's disease, nevertheless plasma electrolytes were not reduced, nor did prolongation of salt restriction for an additional three days produce symptoms of adrenal insufficiency or a reduction of concentration of plasma electrolytes. The response in this case must be regarded apparently as falsely positive. This possibly may be related to abnormality in absorption of salt and water resulting from carcinoma of the stomach, an observation that has been made by others.<sup>6</sup>

The exclusion of Addison's disease in 20 of the foregoing group of 44 patients was of particular importance because a diagnosis of Addison's disease had been made prior to the appearance of the patients at the Mayo Clinic. In a number of instances extensive and expensive treatment had been instituted. On none of these patients did the discontinuance of treatment for the supposed adrenal insufficiency have any deleterious effect. Subsequently several of this group of 20 were subjected to operation, which was tolerated without incident.

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5. Snell, A. M.: Tropical and Nontropical Sprue (Chronic Idiopathic Steatorrhea): Their Probable Interrelationship, *Ann. Int. Med.* **12**:1632-1671 (April) 1939.

6. Fasching, H.: Wasserstoffionenkonzentration und Aciditätsquotient des Harns im Diagramm beim Magenkrebs, *Ztschr. f. d. ges. exper. Med.* **107**:641-646 (May) 1940. Müller, A., and Saxl, P.: Die Chlorausscheidung im Harn und ihre Beziehungen zu den Verdauungsvorgängen, *Ztschr. f. klin. Med.* **56**:546-599, 1905.

## COMMENT

The data presented serve to confirm the finding of Cutler, Power and Wilder that the concentration of chloride in a specimen of urine collected during the last four hours of the fifty-two hour period of salt restriction prescribed by them will indicate, with few exceptions, the presence or absence of Addison's disease. Further confirmation of their results is found in recent reports by several other investigators who also have used the procedure (Ryan and McCullagh,<sup>7</sup> Dryerre,<sup>8</sup> Thorn and Firor<sup>9</sup> and Stephens<sup>10</sup>). The concentration of sodium in the four hour specimen of urine may be somewhat more significant than that of chloride, as Dryerre has suggested and as was noted also by Cutler, Power and Wilder. Practically, however, determinations of the concentration of chloride in urine usually are significant, and only rarely will data for sodium in the urine or for sodium and chloride in the plasma be necessary. The procedure is much less dangerous than the six day period of restriction of salt proposed earlier<sup>11</sup> as an aid in the diagnosis of Addison's disease, the use of which has been attended by at least 2 deaths.<sup>12</sup> Nevertheless, the shorter procedure is not without risk and should be employed only under the most carefully controlled conditions. It should not be attempted unless the clinician is prepared to recognize and treat acute adrenal cortical insufficiency if it should occur.

The greatest usefulness of the study of response to restriction of salt has been in the examination of that rather large group of subjects who complain of fatigability, exhaustion and so forth. The evidence

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7. Ryan, E. J., and McCullagh, E. P.: Desoxy-Corticosterone Acetate in Addison's Disease with Presentation of a Typical Case, *Cleveland Clin. Quart.* **7**:19-23 (Jan.) 1940. McCullagh, E. P., and Ryan, E. J.: The Use of Desoxycorticosterone Acetate in Addison's Disease, *J. A. M. A.* **114**:2530-2537 (June 29) 1940.

8. Dryerre, H. W.: Addison's Disease: The Diagnostic Significance of the Sodium and Chloride Content of the Blood and Urine, *Edinburgh M. J.* **46**:267-277 (April) 1939.

9. Thorn, G. W., and Firor, W. M.: Desoxycorticosterone Acetate Therapy in Addison's Disease: Clinical Considerations, *J. A. M. A.* **114**:2517-2525 (June 29) 1940.

10. Stephens, D. J.: Pituitary and Adrenocortical Insufficiency: The Use of Sodium Chloride in the Treatment of Hypopituitarism, *J. Clin. Endocrinol.* **1**:109-112 (Feb.) 1941.

11. Harrop, G. A.; Weinstein, A.; Soffer, L. J., and Trescher, J. H.: The Diagnosis and Treatment of Addison's Disease, *J. A. M. A.* **100**:1850-1855 (June 10) 1933.

12. Lilienfeld, A.: The Use of the Low Salt Diet in the Diagnosis of Addison's Disease, *J. A. M. A.* **110**:804-805 (March 12) 1938. Garvin, C. F., and Reichle, H. S.: Death Presumably Due to the Use of the Salt Restriction Test in the Diagnosis of Addison's Disease, *Ann. Int. Med.* **14**:323-324 (Aug.) 1940.

shows that if adrenal cortical insufficiency is present in any of these subjects, it has not progressed to the stage of detectable abnormality in the excretion of electrolytes characteristic of the real insufficiency seen in Addison's disease. In this respect it is of interest to note that in the examination by means of the fifty-two hour salt restriction procedure of 60 patients with pulmonary tuberculosis Thorn, Howard and Dayman<sup>13</sup> encountered only 2 instances in which the response might be interpreted as suggesting the presence of adrenal insufficiency.

The consistency of response to the regimen imposed seems rather remarkable considering the number of biologic variables that must be involved. In general, however, the results are in harmony with prevailing evidence that one of the most important abnormalities in Addison's disease is excessive excretion of sodium (and chloride) and disturbance in the metabolism and the excretion of potassium. Thus, despite the intake of considerable amounts of water during the last four hours of the fifty-two hour period, the patient who has Addison's disease will excrete almost always a relatively small volume of urine, but with it as much sodium and chloride as or usually considerably more than would be excreted under similar conditions by the subject who does not have Addison's disease. The restriction of salt and the administration of potassium may not be critical factors in the mechanism of this response. In fact, we have observed that the excretion of urine and electrolytes after the administration of water under much simpler conditions than those described will usually provide information as to the presence or absence of adrenal cortical insufficiency of the degree seen in Addison's disease.<sup>14</sup> At the present time this simplified procedure is being used more and more at the Mayo Clinic as an aid in the recognition or exclusion of Addison's disease.

#### SUMMARY

The results of the examination of 63 additional patients by means of a fifty-two hour salt restriction procedure are reported.

Of 16 patients with Addison's disease, symptoms of crisis which necessitated discontinuance of the test developed in 10; 5 patients responded with the typically high concentrations of chloride and sodium in the final four hour specimen of urine, while 1 patient who responded atypically was found to have concentrations of sodium and chloride in the plasma which were sufficiently low to be diagnostically significant.

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13. Thorn, G. W.; Howard, R. P., and Dayman, H.: *Electrolyte Changes in Pulmonary Tuberculosis, with Special Reference to Adrenal Cortical Function*, Bull. Johns Hopkins Hosp. **67**:345-364 (Nov.) 1940.

14. Robinson, F. J.; Power, M. H., and Kepler, E. J.: *Two New Procedures to Assist in the Recognition and Exclusion of Addison's Disease: A Preliminary Report*, Proc. Staff Meet., Mayo Clin. **16**:577-583 (Sept. 10) 1941.

With 1 exception 44 patients not having Addison's disease responded with typically low concentrations of sodium and chloride in the final four hour specimen of urine. In the exception noted the presence of normal concentrations of sodium and chloride in the plasma and the failure of the patient to react unfavorably to a prolongation of salt restriction aided in the exclusion of the diagnosis of Addison's disease.

Three patients who had Addison's disease and who received desoxycorticosterone acetate through the test procedure gave a response similar to that of subjects who did not have Addison's disease.

The test subjects the patient who has Addison's disease to some danger. Its chief value lies in the diagnosis of or exclusion of adrenocortical insufficiency when uncertainty exists. The clinician who subjects a patient to this test should be prepared to recognize and treat acute adrenal cortical insufficiency should it occur.

# Progress in Internal Medicine

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## SYPHILIS

REVIEW OF THE RECENT LITERATURE

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AND

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The material for this article has been selected mainly from publications which have appeared from July 1940 to November 1941. As in previous reviews,<sup>1</sup> it has been necessary rigidly to select material. Little attention has been paid to reports dealing with comparative serologic studies, and case reports have been almost entirely eliminated. Because of the difficulty of obtaining journals from the European continent, there is a striking decrease in the number of foreign articles reviewed.

### NEW BOOKS

Since the publication of the last review, several important contributions have appeared in monographic form.

Worster-Drought<sup>2</sup> is responsible for a brief (241 pages) monograph entitled "Neurosyphilis." The book is a satisfactory condensation of the subject, more useful to the medical student and the general practitioner than to the specialist.

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From the Syphilis Division of the Medical Clinic, the Johns Hopkins University and Hospital.

1. (a) Moore, J. E.: Syphilis: A Review of the Recent Literature, *Arch. Int. Med.* **56**:1015 (Nov.) 1935. (b) Padget, P., and Moore, J. E.: Syphilis: A Review of the Recent Literature, *ibid.* **58**:901 (Nov.) 1936; (c) **60**:887 (Nov.) 1937. (d) Padget, P.; Sullivan, M., and Moore, J. E.: Syphilis: A Review of the Recent Literature, *ibid.* **62**:1029 (Dec.) 1938. (e) Moore, J. E., and Mohr, C. F.: Syphilis: A Review of the Recent Literature, *ibid.* **64**:1053 (Nov.) 1939. (f) Mohr, C. F.; Padget, P., and Moore, J. E.: Syphilis: A Review of the Recent Literature, *ibid.* **66**:1112 (Nov.) 1940.

2. Worster-Drought, C.: *Neurosyphilis*, London, John Bale & Staples, Ltd., 1940.

Dennie and Pakula<sup>3</sup> are the authors of "Congenital Syphilis." There is, as the preface says, much need for a "book . . . helpful not only to specialists in social [sic] diseases, but also to the family physician." Unfortunately, accomplishment falls far short of aim, since the book is presented in a confused fashion and is regrettably inaccurate. A major defect is disregard of important recent contributions to the problem of diagnosis of syphilis in the newborn. Although the roentgenographic diagnosis of congenital syphilis is discussed at confused length and many of the older publications on the subject are summarized in detail, current literature in the field is overlooked. No mention is made of the lesions which frequently appear in the long bones of infants born of syphilitic mothers treated with a bismuth compound during pregnancy. Other omissions render the discussion of this important subject quite valueless. Further salient criticisms include confusion in arrangement of the subject matter; a curious classification of certain manifestations of the disease, for example, "complete and incomplete central nervous system syphilis"; the inclusion of such material concerned only with acquired syphilis in the adult, and the insertion of many tables in poorly organized and unintelligible statistical form.

A second edition of Moore's<sup>4</sup> "Modern Treatment of Syphilis" has just appeared, this time with the important collaboration of Kemp, Eagle, Goodwin and Padget. By comparison with the first edition, the book suffers from an additional 139 pages (it now contains 674 pages), though this was necessitated by the addition of new material and complete revision of many chapters.

The book likely to attract the most public attention is that by Parran and Vonderlehr,<sup>5</sup> respectively Surgeon General and Assistant Surgeon General, United States Public Health Service, entitled "Plain Words about Venereal Disease." This book is so important as to deserve extended review in the section "Syphilis and National Defense."

#### HISTORY OF SYPHILIS

To Kemp,<sup>6</sup> who died recently, a concise but all-inclusive article on the history of syphilis seemed justified from three points of view:

. . . (1) to review dispassionately the heated arguments as to the origin of syphilis, not so much from the standpoint of the specially trained *medical historian*

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3. Dennie, C. C., and Pakula, S. F.: *Congenital Syphilis*, Philadelphia, Lea & Febiger, 1940.

4. Moore, J. E.: *Modern Treatment of Syphilis*, Springfield, Ill., Charles C. Thomas, Publisher, 1941.

5. Parran, T., and Vonderlehr, R. A.: *Plain Words About Venereal Disease*, New York, Reynal & Hitchcock, Inc., 1941.

6. Kemp, J. E.: *Outline of History of Syphilis*, *Am. J. Syph., Gonorr. & Ven. Dis.* **24**:759 (Nov.) 1940.

but rather from that of the clinician; (2) to present the high lights of development of knowledge regarding syphilis during the 447 years of its familiarity to physicians; (3) to compile a compact bibliography of readily accessible titles, most of which as originals or translations are now available in modern languages.

Most of the paper is devoted to brief discussions of important developments in the field of syphilis from the early descriptions of the disease up to the present time. As to the origin of syphilis, Kemp notes the controversy over the interpretation of three Spanish articles describing the first outbreak of syphilis in Spain and states:

It is now generally believed that syphilis was carried to Europe by the sailors of Columbus when they returned from Haiti to Palos in 1493. One of the leading antagonists at present to this theory is Holcomb, who concludes . . . that syphilis was prevalent in Europe prior to the return of Columbus. Pusey, on the other hand, after an equally careful study of [Holcomb's] sources, believes . . . that syphilis originated in America or was brought from America to Europe. Without an intimate and critical knowledge of these documents, it is impossible, therefore, either to accept or reject the information they present concerning the origin of syphilis.

#### SPIROCHAETA PALLIDA

*Staining.*—Periodically there appear reports of a maturation form of the spirochete of syphilis. Simon and Mollinedo<sup>7</sup> believe they have demonstrated by silver stain a granular form of *S. pallida* from the lymph nodes of 28 of 30 treated and untreated patients with early syphilis. No proof is offered that the granules described were actually a form of *S. pallida*. Rabbit inoculation with a filtrate was not performed.

*Culture.*—Wile and Snow<sup>8</sup> report the results of a series of experiments on culturing *S. pallida* on the chorioallantoic membrane and in the embryo of the developing hen egg. In the original experiment they used material from syphilomas of rabbits infected with the Nichols strain of *S. pallida* as the inoculum and determined the infectiousness of the developing embryo by injecting ground-up material from the chorioallantoic membrane, the embryo itself or both intratesticularly into normal rabbits. Two of the original series of experiments were successful in that syphilitic testicular nodules developed two and two and a half months later, respectively, in the rabbits given injections of tissues of embryos inoculated eight days previously with *S. pallida*. In these experiments dark field examination of some of the same material used for inoculation failed to reveal the presence of organisms.

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7. Simon, C., and Mollinedo, R.: Diagnostic de la syphilis par la recherche du granule spirochétogène, *Presse méd.* 48:513 (May 21) 1940.

8. Wile, U. J., and Snow, J. S.: The Chick Embryo as a Culture Medium for *Spirocheta Pallida*, *J. Invest. Dermat.* 4:103 (April) 1941.

Encouraged by these early successes, the authors repeated experiments to determine the relative infectiousness for the chick embryo of material from rabbit testicular syphilomas and of that from the lymph nodes of syphilitic rabbits, and also, in case of survival of the organism, to differentiate that portion of the developing embryo and the chorio-allantoic membrane which afforded the site for the propagation of the spirochete. The results were entirely negative in that there was no demonstration of persistence of infectiousness under the conditions of the experiment.

Wile and Snow point out that the two successful experiments may represent simple survival of infectiousness rather than any actual propagation of the organism in the developing embryo. They feel, however, that the survival of infectious material in the tissues of chick embryos for eight days in the absence of morphologically typical *S. pallida* demonstrable by dark field examination is suggestive, but not conclusive, evidence of a resting or ultramicroscopic phase of the organism.

Finally, they point out that in the two successful experiments the inoculated eggs were incubated at a temperature of 35 C., while in the unsuccessful experiments the incubation was carried out at temperatures of 37 to 37.5 C. Whether this is accidental association or a lead worthy of further investigation the authors leave as an open question, but they suggest that if and when similar work is carried out, the inoculated eggs should be incubated at carefully regulated temperatures ranging from 20 to 37 C.

#### EXPERIMENTAL SYPHILIS

*Immunity in Syphilis.*—Reynolds,<sup>9</sup> realizing that a susceptible animal host infected with syphilis is resistant to reinfection, studied the fate of organisms of a homologous strain of *S. pallida* inoculated into infected and resistant rabbits. He asks: "Do they [the spirochetes] permeate the tissues of the host as a 'symptomless reinfection,' or are they destroyed by the immune mechanisms of the host; and if so, where and how?"

To decide the point, Reynolds used two groups of rabbits: (a) normal controls and (b) animals which had been treated intensively with arsphenamine late in the course of syphilitic infection. The latter animals, on the basis of previous experience, were considered to be immune and sterilized of spirochetes. Eight normal and 10 immune rabbits were inoculated by subcutaneous implantation of a piece of testis about 1.5 cm. in diameter on the inner aspect of the left thigh. Each piece of testis was removed at the height of acute orchitis and was demonstrated to contain many actively motile spirochetes. At

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9. Reynolds, F. W.: Fate of *Treponema Pallidum* Inoculated Subcutaneously into Immune Rabbits, Bull. Johns Hopkins Hosp. 69:53 (July) 1941.



intervals of two, four, eight, fourteen and twenty-one days, pieces of the implant were removed, macerated separately and suspended in physiologic solution of sodium chloride. A portion of the suspension was examined with dark field microscope and the remainder divided into two equal parts and inoculated intratesticularly into each of 2 normal rabbits. At the end of twenty-one days the left inguinal lymph node was removed from all rabbits who did not have actively motile spirochetes in the portion of the implant removed. Suspensions of these nodes were in turn divided and injected into 2 normal rabbits. In the normal control group of rabbits the spirochetes readily penetrated the regional lymphatics and remained viable in the implant for fourteen days. The regional lymph nodes removed from these rabbits and injected into control rabbits produced characteristic syphilitic infection. In the immune rabbits no pathogenic spirochetes were ever demonstrated in the inguinal lymph nodes by transfer method. *S. pallida* could be demonstrated in the implant by dark field examination up to four days after implantation but only up to two days by transfer to normal rabbits. Reynolds concludes:

On the basis of these experimental results, it seems probable that in the immune rabbit, subcutaneously-inoculated *T. pallida* of homologous strain do not permeate the lymphatics, but are localized at the site of inoculation and subsequently destroyed by the immune mechanisms of the host. The actual mobilization and destruction of spirochetes is probably accomplished by a local antigen-antibody reaction, as immune antibodies are gradually brought into contact with the invading organism.

If rabbits infected with syphilis are adequately treated before the forty-fifth week of infection, that is, before they have acquired specific resistance to the infection, they may at a later date be reinfected with the homologous strain of the organism. If, however, treatment is begun between the forty-fifth and the ninetieth day only a portion of the animals can be reinfected, whereas if the animals are not treated until after the ninetieth day of infection they acquire sufficient immunity to the disease to prevent further infection with the homologous strain. One must therefore conclude that if a syphilitic rabbit is vigorously treated before specific immunity to the infection develops, this treatment is sufficient to prevent subsequent development of specific immunity by the animal.

Schamberg<sup>10</sup> wonders what happens to the development of specific resistance in rabbits treated early in the course of infection with anti-syphilitic drugs or with fever in amounts inadequate to bring about sterilization of the lymph nodes. He states:

The results of the experiments reported above are clear cut. As judged by the occurrence of generalized lesions following treatment, or by the response to a

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10. Schamberg, I. L.: The Effect of Early Subcurative Arsenical and Thermal Treatment on the Development of Specific Immunity in Syphilitic Rabbits, *Am. J. Syph., Gonorr. & Ven. Dis.* **24**:401 (July) 1940.

second inoculation with the homologous strain of *T. pallidum*, no evidence was obtained that subcurative treatment, whether arsenical or thermal, exerted any inhibiting influence on the development of specific resistance against the infecting organism. Those animals which could be proved not to have been cured were shown to be resistant to a second infection and the incidence of generalized lesions in this group was not significantly different from that in the untreated controls, while the animals which were apparently cured, as judged by negative lymph node transfer, were almost uniformly susceptible to a second infection with the homologous strain of *T. pallidum*. The conclusion to be drawn from these results is that subcurative treatment given early in the course of syphilitic infection in rabbits does not prevent the ultimate development of specific immunity to the disease.

*Effect of Estrogen on Syphilitic Infection.*—Frazier and Hu<sup>11</sup> outline the preparation of a potent estrogenic substance obtained from the urine of pregnant Chinese women and describe the changes produced by this substance in the adult male rabbit. They<sup>12</sup> then report the effects of this estrogen on rabbit syphilis. Forty rabbits were used in the experiment. Twenty were given either 20 to 60 rat units of estrogen daily for fifteen days or 30 rat units daily for seventy-six days before inoculation with *S. pallida*. The effect of this substance on the course of the syphilitic infection was the same regardless of whether the animals were treated for fifteen or for seventy-six days before inoculation. Twenty rabbits were left untreated and served as controls. In comparing the course of syphilis in the treated animals with that in the controls, the authors note that in the former group the early manifestations of syphilis were milder, the disease followed a shorter course and generalized foci of infection were less frequent. The most striking modification of the reaction to infection was the resistance to disease developed in the testis.

*Syphilis and Yaws.*—Longley, Clausen and Tatum<sup>13</sup> bring out the fact that while considerable work has been done on the comparative pathogenic and immunologic aspects of yaws and syphilis in rabbits and monkeys, there is less comparable information as to therapy. In order to determine the therapeutic effect of a single injection of either mapharsen or neoarsphenamine on rabbit yaws and rabbit syphilis, the

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11. Frazier, C. N., and Hu, C.: Increased Resistance to Syphilis in the Rabbit Following Prolonged Administration of Urinary Estrogens: I. Feminizing Effects of Estrogens on Adult Male Rabbits, *Endocrinology* **28**:283 (Feb.) 1941.

12. Frazier, C. N., and Hu, C.: Increased Resistance to Syphilis in the Rabbit Following Prolonged Administration of Urinary Estrogen: II. Character of the Reaction to *Treponema Pallidum* in Feminized Male Rabbits, *Endocrinology* **28**:294 (Feb.) 1941.

13. Longley, B. J.; Clausen, N. M., and Tatum, A. L.: Comparison of Response of Yaws and Syphilis in Rabbit to Mapharsen (Arsenic Preparation) and Neoarsphenamine, *J. Pharmacol. & Exper. Therap.* **71**:49 (Jan.) 1941.

authors treated animals inoculated with the Nichols strain of *S. pallida* and ones inoculated with a strain of yaws obtained from Chesney. Seven days after single injections of one of the arsenical drugs into these animals, the resultant testicular lesions were removed; each was minced, suspended in physiologic solution of sodium chloride and reinjected intratesticularly into 2 recipient rabbits. The latter were observed for eight to twelve weeks for the appearance of lesions or a positive serologic reaction of the blood. The original treated rabbit was considered cured if a syphilitic lesion or a positive serologic reaction did not develop in the recipient rabbit. There was found to be no significant difference between the therapeutic response of the two diseases to single injections of neoarsphenamine or mapharsen. The therapeutic index of a single dose of neoarsphenamine was superior to that of a single dose of mapharsen both in rabbit yaws and in rabbit syphilis. The authors state: "The rabbit tolerates 150 mgm. per kilogram of neoarsphenamine and mapharsen is tolerated at only 10 mgm. per kilogram, whereas the single minimal curative doses are 13 and 5, respectively." They recognize that equal susceptibility to cure has no necessary bearing on the identity of the two diseases.

*Liver Lipids.*—According to MacLachlan,<sup>14</sup> injections of arsphenamine and neoarsphenamine into rabbits in sufficient dosage to produce severe hepatic necrosis with fatty degeneration failed to cause any changes in the total liver lipids or in the ratio of phospholipids to neutral fat.

*War and Experimental Syphilis.*—The effect of a war on the caliber of medical research is demonstrated by the following articles by Jahnel.<sup>15</sup> This investigator has in the past greatly contributed to the field of experimental syphilis and is generally known as a brilliant and thorough worker. In 1940 and 1941 he published seven articles, of which these three are examples.

Basing his statements on the study of 4 dormice and 2 rabbits inoculated with syphilis, Jahnel concludes that starvation has no beneficial effect on the course of the experimental disease. He treated 3 syphilitic rabbits with the venom of a species of European viper and concluded that it had no effect on the course of the disease. In another experiment Jahnel found that the venoms of three species of poisonous

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14. MacLachlan, P. L.: Effect of Arsenicals on Liver Lipids of Rabbits, *Proc. Soc. Exper. Biol. & Med.* **44**:429 (June) 1940.

15. Jahnel, F.: Experimentelle Untersuchungen über den Einfluss des Hungerns auf den Syphilisverlauf, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **98**:97 (June 12) 1940; Untersuchungen über die Einwirkung des Giftes der Sandotter *Vipera ammodytes ammodytes* Linnaeus bei experimenteller Syphilis, *ibid.* **98**:144 (June 12) 1940; Ueber die Unwirksamkeit verschiedener Schlangengifte bei experimenteller Syphilis, *ibid.* **98**:344 (Sept. 28) 1940.

snakes (*Bungarus fasciatus*, *Lachesis lanceolatus* and *Vipera lebetina* Linnaeus) had no effect on the course of experimental syphilis in 3 rabbits.

#### SERODIAGNOSIS OF SYPHILIS

*Antigen.*—Brown and Kolmer<sup>16</sup> have attempted, as many others have before them, to identify the active principle of the antigen used in the serodiagnosis of syphilis. Without accomplishing their aim, they were able to add the negative information that the antigenic principle is neither lecithin nor cephalin but is some substance absorbed in equal proportions by both.

*Cultured Spirochetes as Antigen in Serologic Tests for Syphilis.*—Kolmer, Kast and Lynch<sup>17</sup> have further investigated the role played by cultured spirochetes in the serologic reactions for syphilis. They summarize their results as follows:

The absorption of human syphilitic sera with Kahn antigen removed all antibody or reagin concerned in the Wassermann and flocculation tests but did not remove the complement fixing antibody for antigens of cultures of various strains of spirochetes, including alleged cultures of *S. pallida*.

Absorption of human syphilitic sera with spirochetes removes complement-fixing antibody for them, but not the antibody or reagin concerned in the Wassermann and flocculation reactions.

Absorption of a normal rabbit serum giving nonspecific positive Wassermann and Kline reactions with spirochetes (Reiter strain) did not remove the Wassermann antibody or reagin. Absorption of three normal rabbit sera giving positive complement fixation and agglutination reactions with an antigen of the Reiter strain, however, largely removed the natural antibody for them.

Agglutinins for various culture strains of alleged *Spirochaeta pallida* are present in syphilitic and nonsyphilitic human sera in practically equal amounts. Especially large amounts were found in all sera for *S. microdentium*. Syphilitic infection does not appreciably increase agglutinins for various strains of cultured spirochetes including alleged strains of *S. pallida*.

Active immunization of rabbits with living and heat-killed vaccines of alleged cultures of *S. pallida* and other spirochetes produces large amounts of agglutinin and complement-fixing antibody for antigens of spirochetes but no antibody or reagin for Wassermann antigen. The agglutinins were fairly specific for homologous strains of spirochetes, but the complement fixation reactions were largely of a group character.

Rabbits immunized with vaccines of living and heat-killed vaccines of the Nichols-Hough strain of *S. pallida* were not protected against syphilitic infection when inoculated intratesticularly and intracutaneously with homologous virulent *S. pallida* (Nichols-Hough strain).

16. Brown, H., and Kolmer, J. A.: Studies on Chemical Constitution of Antigenic Substance in Alcoholic Tissue Extracts Concerned in Serum Diagnosis of Syphilis, *J. Biol. Chem.* **137**:525 (Feb.) 1941.

17. Kolmer, J. A.; Kast, C. C., and Lynch, E. R.: Studies on the Role of *Spirochaeta Pallida* in the Wassermann Reaction: II. The Relation of Spirochetal Antibodies to the Wassermann Reagin, *Am. J. Syph., Gonor. & Ven. Dis.* **25**:412 (July) 1941.

Tryptic digests of two strains of *S. pallida* were antigenic in complement fixation tests with human syphilitic and rabbit antispirechetral sera.

Precipitates obtained from tryptic digests after treatment with alcohol (F68 fractions) were likewise antigenic in complement fixation tests with human syphilitic and rabbit antispirechetral sera. The results may be due to the presence of lipoids.

An alcoholic extract of the Reiter strain was likewise antigenic in tests with human syphilitic sera, presumably due to the presence of lipoids.

An antigen of the alcoholic extracted spirochetes was not antigenic in complement fixation tests with human syphilitic sera, presumably due to the absence of lipoids.

Their practical conclusion is that spirochetral complement fixation antigens are both less specific and less sensitive than standard beef heart lipid antigens. These results are at variance with data concerning the specificity and sensitivity of "palligen," a German spirochetral antigen, previously published both in Germany and in this country. It is fortunate that a more definitive answer to the questions raised in this important problem should shortly be forthcoming. In an evaluation study of serologic tests sponsored by the United States Public Health Service in the fall of 1941, both Kolmer and Eagle were represented with their respective "pallida" tests, and a direct comparison of specificity and sensitivity based on selected specimens of syphilitic and of non-syphilitic serums will be available in the near future.

*Evaluation of Serologic Tests.*—The Committee on Evaluation of Serodiagnostic Tests for Syphilis<sup>18</sup> presents a comparison of the results of the 1938 and 1939 serologic conferences and draws important general conclusions. They found that many unsatisfactory results in serologic examinations are due to reliance on obsolete technics or to short cuts. The more closely the latest technics of the author-serologists are followed, the better the results.

One fourth of the state laboratories were found to be doing superior work in this field, whereas 30 state laboratories were classed as unsatisfactory in 1938; only 22 were so classed in 1939.

*Interpretation of Serologic Tests.*—Mallory<sup>19</sup> modestly states that he has nothing original to offer, then proceeds to an excellent critical survey of the present state of serologic tests for syphilis, with conclusions which deserve emphasis for their clarity of thought.

The serological diagnosis of syphilis has advanced greatly in the last fifteen years, but there is still no perfect test for the disease. A negative reaction does

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18. Hazen, H. H.; Parran, T.; Mahoney, J. F.; Sanford, A. H.; Senear, F. E.; Simpson, W. M., and Vonderlehr, R. A.: Serodiagnostic Tests for Syphilis as Performed in State Laboratories in 1938 and 1939, *South. M. J.* **33**:633 (June) 1940.

19. Mallory, T. B.: The Interpretation and Reliability of Reports of Serological Tests for Syphilis, *New England J. Med.* **223**:441 (Sept. 19) 1940.

not rule out and a positive one does not prove the presence of syphilis. The percentage of accurate diagnoses can be considerably increased by the use of multiple tests, but in the face of discrepant reports every case requires individual interpretation and the most exact clinical correlation.

Moore and Eagle<sup>20</sup> call attention to the great confusion which exists because of the multiplicity of serologic technics known by the names of their originators. They offer the following practical solution:

The ever increasing number of tests available for the serum diagnosis of syphilis, and the necessity for interpreting conflicts between them, place a burden of evaluation on the physician which, lacking the necessary technical knowledge, he is often not qualified to assume.

Although the standardization of serologic technic is not yet feasible, it is possible to standardize the method of reporting serologic results. In the interests of simplicity, clarity and the best possible utilization of the laboratory data it is therefore recommended that the proper means now used in reporting serologic tests be replaced by the generic term "Serologic Tests for Syphilis" (abbreviated "STS"), of which in routine practice there are three categories: screen flocculation, standard flocculation and complement fixation. It is further recommended that the results of the laboratory findings, whether flocculation or complement fixation tests, single or multiple tests, be reported on an over-all composite basis, as "Serologic Tests for Syphilis—Positive, Doubtful or Negative."

The onus of unifying conflicting laboratory findings is thus placed on the individual best qualified, the laboratory director. No information of diagnostic significance is withheld from the physician, for the reverse of the report sheet will carry a statement as to the results obtained with the individual tests, on which the over-all report is based.

*Quantitative Serologic Tests.*—Moore and Eagle<sup>21</sup> review the available information regarding the use of quantitative serologic tests for syphilis, and from a study of the literature, the analysis of 1,665 personally observed cases and unpublished information they conclude:

The serum of syphilitic patients contains varying quantities of reagin. Quantitative serologic tests to determine this reagin "titer" are comparable only when carried out in the same laboratory by the same technic; and even then, the results may be modified by day-to-day variations in the sensitivity of the test.

The quantitative reagin titer of the blood in 508 patients with early syphilis, determined by a complement fixation technic, varied from 0 to 1600 units of reagin. In primary syphilis, the mean titer was  $104.3 \pm 13.74$  units, the median  $43.2 \pm 17.22$  units; in secondary syphilis the mean was  $179.6 \pm 7.54$  and the median  $142.3 \pm (9.45)$  units.

In 445 patients with various forms of untreated late syphilis, the quantitative titer ranged from 0 to 1600 units. These patients were separated into 5 groups: (a) latent syphilis, (b) various forms of late syphilis (excluding neurosyphilis),

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20. Moore, J. E., and Eagle, H.: The Confusing Multiplicity of Serologic Tests for Syphilis: Standardization of the Serologic Report as a Possible Solution, *J. A. M. A.* **117**:243 (July 26) 1941.

21. Moore, J. E., and Eagle, H.: The Quantitative Serologic Test for Syphilis: Its Variability, Usefulness in Routine Diagnosis, and Possible Significance; a Study of 1,665 Cases, *Ann. Int. Med.* **14**:1802 (April) 1941.

(c) diffuse meningovascular neurosyphilis, (d) general paresis, (e) tabes dorsalis. In these groups, the mean titers ranged from 21.5 to 44.1 units, the medians from 10.7 to 25 units, i. e., significantly lower than in early syphilis. It is suggested by these data, though not yet definitely proved, that patients with late latent syphilis and tabes dorsalis may have significantly lower serologic titers than patients with other types of late syphilis.

In late syphilis, previous treatment in any amount and at any time before quantitative testing significantly reduced the mean and median titers in the 712 such patients tested. This reduction was not necessarily associated with clinical improvement.

Quantitative serologic testing is of little value as a routine diagnostic procedure.

The reagin titer of the blood is not an expression of the severity or gravity of syphilitic infection in the individual patient. Enormous variations in titer are observed in all types of clinical involvement (0-1600), including both early and latent syphilis; and the reduction in titer effected by treatment is not necessarily associated with clinical improvement.

The reagin titer appears definitely to be related to the numbers of organisms present in the tissues of the host, since titers were higher in early than in late syphilis. As between various types of late syphilis, however, no such conclusion is permissible. There is no evidence available as to the possible relationship of reagin titer to the involvement of particular body tissues.

The effect of prolonged treatment on the rate of fall of reagin titer may conceivably be an expression of the immunity or resistance of the host; but even if this were true, a single quantitative test before treatment would be of no diagnostic or prognostic importance. Further studies of the behavior of reagin titer under prolonged treatment are essential to settle the possible prognostic value of such serial quantitative tests.

Crosby and Campbell<sup>22</sup> have studied the quantitative serologic test for syphilis and its response to the first course of arsenical treatment in 526 patients with early syphilis. The authors summarize their results as follows:

In untreated early syphilis, the median reagin titer increases rapidly for the first four weeks after the appearance of lesions, and then (until the twenty-fifth week) remains approximately stationary.

In seronegative primary syphilis, an apparent provocative effect occurs at the second week of treatment, but this phenomenon is not observed in seropositive primary or early secondary syphilis. It is suggested that this provocative effect is more apparent than real, that it occurs only when reagin titer is spontaneously rising, and that in early syphilis, a true arsphenamine provocative effect probably does not occur.

The median initial reagin titer is lower, and declines more rapidly under treatment, in seropositive primary than in early secondary syphilis.

The factors of race, sex, and age do not demonstrably affect initial reagin titer or its response to treatment.

The presence or absence of spinal fluid abnormalities does not appear to influence initial reagin titer or its response to treatment.

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22. Crosby, E. L., and Campbell, A. D.: The Quantitatively Titered Serologic Test in Early Syphilis and Its Response to Treatment, *Am. J. Syph., Gonorr. & Ven. Dis.* 25:566 (Sept.) 1941.

The co-existence of pregnancy and early syphilis has no apparent effect on reagin titer.

Reagin titer is initially higher, and under treatment falls more slowly, in patients with "florid" than in those with "trivial" early secondary syphilis.

Greene and his collaborators<sup>23</sup> have also studied the quantitative serologic test for syphilis and the possible application of quantitative methods as a routine procedure for the control of treatment. They found that quantitative titration eliminated zone reactions entirely and expressed the opinion that for an estimation of treatment results, quantitative tests give a better index than the conventional qualitative reports.

*Occurrence of Reagin or Reagin-Like Substance in the Serum.*—Animals: As early as 1910 reports periodically appeared in the literature describing positive serologic reactions for syphilis occurring in the serum of many domestic and wild animals. Because of recent increased interest in biologic false positive serologic reactions for syphilis, there has been an increased literature in regard to animal serum.

Sherwood, Bond and Clark<sup>24</sup> did serologic tests for syphilis on the serum of eleven different animal species, with a high percentage of positive results in many. They were unable definitely to identify the substance which caused the positive reaction but suggested that it was contained in the globulin fraction of serum, as is syphilitic reagin in human serum.

Greene and Harding<sup>25</sup> did concomitant Kline and heterophile antibody tests on the serum of 134 head of cattle. None gave a clear-cut negative Kline reaction. In only 25 (18.7 per cent) of the cases did the serum agglutinate sheep red blood cells, and in these it did so only in low titers. They conclude that there is no relation between the positive Kline reaction and the presence of heterophile antibody.

Kemp and his collaborators<sup>26</sup> completely reviewed and aptly summed up the literature on this important subject. They also performed serologic tests for syphilis on the serum of many domestic animals. They state:

Personal experience and a review of the literature show that a large number of animals other than man have been found to have positive serologic tests for syphilis. Our findings, using a variety of tests for the examination of the sera

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23. Greene, R. A.; Breazeale, E. L., and Croft, C. C.: A Quantitative Study of Syphilitic Serum, *J. Lab. & Clin. Med.* **25**:972 (June) 1940.

24. Sherwood, N. P.; Bond, G. C., and Clark, H. F.: Results Obtained with Kolmer, Kahn, Kline and Eagle Tests on Animal Sera, *Am. J. Syph., Gonorr. & Ven. Dis.* **25**:93 (Jan.) 1941.

25. Greene, R. A., and Harding, H. B.: Absence of Heterophile Antibodies in Cow Sera and Occurrence of Positive Kline Reactions, *Am. J. Syph., Gonorr. & Ven. Dis.* **25**:89 (Jan.) 1941.

26. Kemp, J. E.; Fitzgerald, E. M., and Shepherd, M.: Occurrence of Positive Serologic Tests for Syphilis in Animals Other Than Man, with Review of Literature, *Am. J. Syph., Gonorr. & Ven. Dis.* **24**:537 (Sept.) 1940.



of numerous animals, are in agreement with those of other observers. Our findings also confirm earlier observations that there is marked discrepancy between the results of the different tests in different animal species and the results of identical tests in the same animal species. Quantitative determination of the amount of the reacting substance in the blood of animals shows that, as determined by the Eagle microflocculation test, it is less in amount than the reagin in the serum of known syphilitics. In two animal species, dogs and cattle, and probably sheep as well, the number of positive tests increased with increasing age of the animals.

We feel as a result of this study that the frequency with which positive tests for syphilis occur in animals other than man is not relevant to the problem as to their validity when they are the only evidence of syphilis in man.

**Human Beings:** The possibility that the serum of man, like that of other animals, might contain reagin or some reagin-like substance in the absence of syphilitic infection has, of course, not escaped the attention of serologists, though little stress has been laid on it. Browning,<sup>27</sup> Meinicke<sup>28</sup> and Hinkleman<sup>29</sup> have all contended that the difference between normal and syphilitic human serum is merely one of degree, and not one of kind, and in that connection have stressed the nonspecific nature of the lipoidal "antigen" and of the "reagin" with which it combines.

In 1931 Malloy and Kahn<sup>30</sup> observed that when normal serum was mixed with standard Kahn antigen, microscopic aggregations formed slowly. No aggregations were visible when the mixture was examined immediately; after it had stood one hour, the average size of the aggregates was 60 square microns and after six hours 190 square microns. In contrast, the average size of the aggregates formed by mixing syphilitic serum with standard Kahn antigen was 420 square microns when the mixture was examined immediately, 1,730 square microns after one hour and 4,260 square microns after six hours.

In 1934 Schreus and Foerster<sup>31</sup> described a method for the demonstration of small quantities of reagin in the serum of syphilitic patients whose blood gave negative Wassermann reactions. When subliminal amounts of a serum of known positive titer, less than would be necessary to give a positive Wassermann reaction, were added to the appar-

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27. Browning, C. H.: *Biochemistry of Immune Reactions*, Brit. M. J. **1**:239, 1915.

28. Meinicke, E.: *Zur Theorie und Methodik der serologischen Luesdiagnostik*, Deutsche med. Wchnschr. **45**:178 (Feb. 13) 1919.

29. Hinkleman, A. J.: *Biochemistry of the Wassermann Reaction*, Am. J. Syph., Gonorr. & Ven. Dis. **11**:594 (Oct.) 1927.

30. Malloy, A. M., and Kahn, R. L.: *The Ultramicroscopic Precipitation Reaction in Syphilis*, J. Infect. Dis. **48**:243 (March) 1931.

31. Schreus, H., and Foerster, R.: *Spezifische Sensibilisierung von serologischen Reaktionen: Grundlage und Methodik der spezifisch sensibilisierten Wassermann-Reaktion (WSR.)*, Ztschr. f. Immunitätsforsch. u. exper. Therap. **82**:53, 1934.

ently negative serum, the latter gave positive results, presumably because of an additive effect. The following year Barnett, Jones and Kulchar,<sup>32</sup> using the Kline test, adapted this technic to the demonstration of reagin in normal serum.

Sherwood and his collaborators,<sup>33</sup> realizing that the sensitivity of a serologic test can be increased if the serum-antigen ratio is increased, adapted this method to study the serum of 1,018 presumably non-syphilitic white college students of both sexes. Using the Kahn test, serum-antigen ratios varying from 100:1 to 1:5 were employed. Serum was also checked with standard technics. One student, found to react positively with all the technics used, was considered to have late latent syphilis and was not included in the study. Of the remaining 1,017 presumably normal, nonsyphilitic students, the serum of 15 was found to give a positive reaction with this special technic, particularly in the higher serum-antigen ratios.

Subsequent serum specimens of 9 of these 15 students were examined. Four had later negative reactions. Even the 5 students whose serum gave a positive reaction on reexamination eventually had negative tests without antisyphilitic treatment. The authors believe that the serum of these 9 normal persons contained a reagin-like substance.

In order to determine the incidence of biologic false positive serologic reactions in normal nonsyphilitic persons, Eagle<sup>34</sup> has had serologic tests for syphilis performed on the serum of 40,545 white college students. He summarizes the results as follows:

1. Serologic tests for syphilis were carried out in twenty-five universities on a total of 40,545 white students of both sexes. Sixty-two (0.15 per cent) gave positive or doubtful tests confirmed by repeat specimens. Twenty-one of these presented clinical evidence or gave a definite history of syphilitic infection, and 5 others had previously received antisyphilitic treatment, with no available data as to why that treatment was instituted.

2. There remained 36 students (an incidence of 1 in 1,125 tested) who gave repeated positive or doubtful serologic tests in the absence of clinical evidence or history of syphilitic infection, and who might therefore possibly be nonsyphilitic persons giving biologic false positive serum tests for syphilis. However, the correlation between the incidence of clinically proved syphilis and these putative false reactions in the individual schools was so high (ungrouped coefficient of correlation 0.83) as to suggest that approximately 26 (70 per cent) of these clinically unconfirmed tests actually represented latent syphilis.

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32. Barnett, C. W.; Jones, R. B., and Kulchar, G. V.: Measurement of Reagin in Nonsyphilitic Sera, *Proc. Soc. Exper. Biol. & Med.* **33**:214 (Nov.) 1935.

33. Sherwood, N. P.; Bond, G. C., and Canuteson, R. I.: Possible Presence of Reagin-Like Factor in Normal Human Serum, *Am. J. Syph., Gonorr. & Ven. Dis.* **25**:179 (March) 1941.

34. Eagle, H.: On Specificity of Serologic Tests for Syphilis as Determined by 40,545 Tests in College-Student Population, *Am. J. Syph., Gonorr. & Ven. Dis.* **25**:7 (Jan.) 1941.

3. It is an open question whether the remaining 10 cases (an incidence of 1 in 4,000 tested) represented latent syphilis, false positive reactions due to an unrecognized intercurrent infection, or biologic false positive tests for syphilis occurring in normal individuals. In any event, the incidence of such reactions in the population tested seems sufficiently small to justify, as a general public health measure, the diagnosis of syphilis in clinically normal individuals on the basis of repeatedly positive serologic tests, even in the absence of history or clinical evidence of syphilitic infection. In the individual case, however, and particularly in population groups in whom the incidence of syphilis is known to be small, attempts are in order to differentiate between a possible biologic false positive test and one actually due to latent syphilitic infection.

*Biologic False Positive Serologic Reactions for Syphilis Associated with Other Diseases.*—Vaccinia: Within recent years it has been suspected that cowpox vaccine might cause a biologic false positive serologic reaction for syphilis, but not until this year has a sufficiently large group of persons been studied. One can now state definitely that this original suspicion was correct.

Thomas and Garrity<sup>35</sup> report Kahn reactions of the blood for 10,000 navy recruits examined between July 1939 and July 1940. Specimens of serum were collected after the recruits were vaccinated with cowpox vaccine. Of the 10,000 specimens, only 12 were found to give persistently positive reactions, an incidence of 0.12 per cent. In addition to these 12 specimens the reactions of which remained persistently positive, 26 others gave strongly positive reactions which became spontaneously negative within three to four weeks. There were also 16 weakly positive or doubtful specimens the reactions of which became negative within a few days. Of the 26 men with false positive serologic reactions, 11 had primary and 12 accelerated reactions to vaccinia, while only 3 were immune to cowpox vaccine.

Reporting on an additional group of 10,000 navy recruits, Thomas and Garrity<sup>36</sup> collected specimens of blood for serologic tests for syphilis only before vaccination. In this group the serum of only 0.06 per cent gave false positive serologic reactions for syphilis, as compared with 0.26 per cent in the previously reported group, who had been vaccinated before the specimens of blood for serologic tests for syphilis were collected.

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35. Thomas, G. E., and Garrity, R. W.: Routine Kahn Blood Reactions: Report of Ten Thousand Tests Made on Naval Recruits, U. S. Nav. M. Bull. **39**:72 (Jan.) 1941.

36. Thomas, G. E., and Garrity, R. W.: Routine Kahn Blood Reactions: Supplementary Report on Twenty Thousand Tests Made on Naval Recruits, with Observations on the Relationship of Cowpox Vaccination to the False Positive, U. S. Nav. M. Bull. **39**:272 (April) 1941.

Lynch, Boynton and Kimball<sup>37</sup> vaccinated 267 students entering a university. Before vaccination each student had a serologic test for syphilis. One student had a frankly positive reaction, and 3 gave doubtful serum reactions. All 4 of these were excluded from the study. An attempt was made to have the 263 students return in two weeks for another serologic test for syphilis, and if the reaction was positive, they were followed regularly until the reaction became negative. Of the 263 students tested, 43 (16 per cent) reacted to one or more of the serologic tests used in the study. In most instances the reaction was either doubtful or weakly positive. In many cases the positive serologic reaction persisted for as long as two months, and in a few instances it was still present after four months. One student was reported to have a doubtful reaction with the Kline test at the end of one hundred and sixty-four days. The Kahn verification test performed on 2 specimens from the same student gave a syphilitic type of reaction. This is the second reported instance in which the Kahn verification test has failed to demonstrate a biologic false positive reaction due to vaccinia.

Infectious Mononucleosis: Werlin and his collaborators<sup>38</sup> report on 21 patients with infectious mononucleosis. Four patients gave positive reactions to one or more serologic tests for syphilis; all 4 were deemed to be nonsyphilitic.

According to Kaufman,<sup>39</sup> the incidence of false positive serologic reactions for syphilis in patients with infectious mononucleosis is difficult to determine with any degree of accuracy. His series consists of 82 patients with infectious mononucleosis, of whom 64 had one or more serologic tests for syphilis. In half of these the test was repeated at least once. Among these 64 patients, 3 had false positive serologic reactions for syphilis. It is interesting to note that in 2 patients known to have congenital syphilis with negative serologic reactions of the blood following treatment, the Wassermann reaction did not revert to positive during the course of infectious mononucleosis.

In the course of comments on the nature of the antibody response in infectious mononucleosis, Warren<sup>40</sup> observes that false positive reactions to Wassermann, Kahn and Eagle tests are frequent.

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37. Lynch, F. W.; Boynton, R. E., and Kimball, A.: False Positive Serologic Reactions for Syphilis Due to Smallpox Vaccinations (Vaccinia), *J. A. M. A.* **117**:591 (Aug. 23) 1941.

38. Werlin, S. J.; Dolgopel, V. B., and Stern, M. E.: Infectious Mononucleosis: A Diagnostic Problem, *Am. J. M. Sc.* **201**:474 (April) 1941.

39. Kaufman, R. E.: False Positive Serologic Reactions for Syphilis in Infectious Mononucleosis, *J. Lab. & Clin. Med.* **26**:1439 (June) 1941.

40. Warren, E. W.: Observations on Infectious Mononucleosis, *Am. J. M. Sc.* **201**:483 (April) 1941.

Sadusk<sup>41</sup> reviews the literature both on cutaneous eruptions and on false positive serologic reactions for syphilis in infectious mononucleosis. He calls attention to the difficulty which may be encountered in differentiating secondary syphilis from infectious mononucleosis when in the latter disease there are a cutaneous rash and a positive serologic reaction for syphilis. He mentions the various clinical and laboratory tests which may be of aid, such as absence of rash on the hands and feet, a blood picture characteristic of infectious mononucleosis, a positive Paul-Bunnell reaction and the presence of *S. pallida* in the cutaneous lesions. He reports 4 cases, in 1 of which the rash was morbilliform, in 1 maculopapular and in 2 macular. Doubtful or positive serologic reactions for syphilis were present in all cases.

Leprosy: An attempt has been made by Eagle, Hogan, Mohr and Black<sup>42</sup> to differentiate biologic false serologic reactions for syphilis from true reactions in leprosy patients. For this study, 41 male lepers were selected. Not only was serum obtained for serologic study, but each patient was thoroughly examined clinically in an attempt to rule out syphilitic infection. The serum of 37 patients gave positive reactions for syphilis. The authors summarize their observations on the serum of these 37 patients as follows:

Of 37 leprosy patients giving positive Eagle microfloculation tests in the absence of history or clinical evidence of syphilitic infection, 25 also gave positive Wassermann tests, and only 6 gave positive complement fixation tests with a suspension of cultured spirochetes. Since the spirochetal complement fixation test is a sensitive diagnostic test for syphilis, it apparently permits the identification as biologic false reactions of most of the positive Wassermann and flocculation tests obtained in leprosy patients in the absence of syphilitic infection.

It was further found that there was a difference in the serologic reactivity of Wassermann-positive syphilitic and leprosy sera, in that the latter tended to give a disproportionately high titer in a Wassermann as compared with a flocculation test. Of the 19 patients in this series in whom both tests were positive, the Wassermann titer was on the average seven times higher than the flocculation titer.

Of the 6 sera in this series which reacted positively to the spirochetal antigen, three had disproportionately high Wassermann titers, with the spirochetal complement fixation tests barely positive. These three sera probably represent biologic false spirochetal reactions caused by leprosy. In the remaining 3 patients, however, relatively high titers were obtained in all three tests (Wassermann, flocculation, and spirochetal complement fixation), a serologic "pattern" approaching that observed in most syphilitic sera. The possibility must therefore be considered that these 3 patients were actually syphilitic.

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41. Sadusk, J. F., Jr.: The Skin Eruption and False-Positive Wassermann in Infectious Mononucleosis (Glandular Fever), *Internat. Clin.* **1**:239 (March) 1941.

42. Eagle, H.; Hogan, R. B.; Mohr, C. F., and Black, S. H.: On the Reactivity of the Serum and Spinal Fluid of Leprosy Patients with Spirochetal Suspensions, *Am. J. Syph., Gonorr. & Ven. Dis.* **25**:397 (July) 1941.

Twenty-nine leprous patients giving negative Wassermann and flocculation tests were also negative to the spirochetal complement fixation test.

Spinal fluids obtained from 9 leprous patients with positive serum tests for syphilis (3 of whom also gave positive spirochetal tests) were completely negative to all tests used (Wassermann, flocculation, and spirochetal complement fixation).

**Malaria:** Eagle, Mays, Hogan and Burney<sup>43</sup> studied the serum of 11 nonsyphilitic patients inoculated with tertian malaria. Specimens of blood were collected at regular intervals before and after inoculation and after the administration of quinine. The specimens of serum were identified by code numbers and could not be distinguished from 6 control specimens of serum from nonmalarial persons, 3 of whom were normal and 3 syphilitic. Each specimen of serum was tested by a complement fixation technic, using as the antigen a washed suspension of cultured spirochetes; by the Eagle microfloculation technic and by the Eagle modification of the Wassermann technic. Seven of the 11 patients gave biologic false positive reactions with the routine serologic tests for syphilis used in this experiment, and 9 gave positive reactions with the complement fixation test, employing the spirochetal antigen. The authors therefore conclude that the spirochetal complement fixation does not permit a serologic differentiation of syphilis and malaria.

*Methods of Differentiating False Positive from True Positive Reactions.*—Moore, Eagle and Mohr<sup>44</sup> have outlined a method of approach to the differentiation of the biologic false positive serologic reaction from the positive result due to the presence of syphilitic infection. When a biologic false positive reaction is suspected, the following procedure is suggested:

Take a careful history as to (a) symptoms of some intercurrent infection of whatever nature, (b) serum treatment (including tetanus antitoxin) or (c) vaccination within the four months preceding the questionable serologic test. . . .

Make a careful physical examination for evidences of acute infection preceding the questionable serologic test, with special reference to lymph nodes, spleen and lungs. . . .

Make a thorough search of blood smears for malarial parasites. . . .

Examine blood smears for infectious mononucleosis. . . .

Make a blood test for heterophile antibody (the Paul-Bunnell test). . . .

Determine the sedimentation rate. The sedimentation rate is thought to be considerably increased in early syphilis and in neurosyphilis; it may be normal or, more frequently, slightly increased in late and in latent syphilis. Also it is

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43. Eagle, H.; Mays, J. R. S.; Hogan, R. B., and Burney, L. E.: The Reactivity of the Serum of Malarial Patients with Spirochetal Suspensions, *Am. J. Syph., Gonorr. & Ven. Dis.* **25**:406 (July) 1941.

44. Moore, J. E.; Eagle, H., and Mohr, C. F.: Biologic False Positive Serologic Tests for Syphilis: Suggested Method of Approach to Their Clinical Study, *J. A. M. A.* **115**:1602 (Nov. 9) 1940.

frequently increased to an even greater degree in many of the acute infections, which may be responsible for false positive serologic reactions. . . .

Repeat serologic tests for syphilis by several different technics including both complement fixation and flocculation, at least one of which is quantitatively titered. . . .

Repeat serologic test for syphilis in several different laboratories of known excellence in order to rule out all possibility of technical error. . . .

Perform the Kahn "verification" test. . . .

Test the patient's serum by complement fixation with spirochetal antigen (the Reiter or Kayan strain of cultured *Spirochaeta pallida*). . . .

Test the patient's serum with wholly nonspecific antigens, such as those prepared from bacteria (the gonococcus, staphylococcus, tubercle bacillus) or from such substances as milk and lecithin. . . .

Carry out a prolonged serologic follow-up (weeks or months) by a good quantitative technic, testing the blood at frequent intervals without instituting anti-syphilitic treatment. . . .

Examine members of the family and sexual contacts. This step in the examination may be extremely important. . . .

Examine the cerebrospinal fluid if a decision cannot be reached earlier. When there are genuine reasons for believing that the positive results are false, do not adopt spinal puncture as the first step in the investigation, since often a clearcut [explanation] (e. g. of infectious mononucleosis) can be found for the supposed false positive result. . . .

The so-called provocative procedure (injection of an arsphenamine with following quantitative serologic testing daily for fourteen days) is in our opinion worthless. . . .

Finally, withhold antisyphilitic treatment unless and until the diagnosis of syphilis is proved. Such treatment is dangerous and should not be given unless the risk is justified by the actual existence of syphilis.

The authors summarize their statements as follows:

From an outline of a method of approach to the differentiation of the biologic false positive serologic reaction from the positive result due to the presence of syphilitic infection, it is obvious that many of the suggested procedures require special clinical or laboratory expertness and that the final decision as to the presence or absence of syphilis in a given case is a highly individualized problem which often requires weeks or months of observation and expert syphilologic advice.

Kahn and associates report the results of the Kahn verification test with the serum of lower animals,<sup>45</sup> of syphilitic human beings<sup>46</sup> and of human beings suspected of having a false positive standard reaction.<sup>47</sup> The author believes that with the verification test the serum of

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45. Kahn, R. L.; McDermott, E. B., and Marcus, S.: Effect of Temperature on Kahn Reaction, with Serologically Positive Sera of Lower Animals, *Am. J. Syph., Gonorr. & Ven. Dis.* **25**:151 (March) 1941.

46. Kahn, R. L.; McDermott, E. B., and Marcus, S.: Effect of Temperature on Kahn Reaction, with Serologically Positive Sera of Human Syphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **25**:157 (March) 1941.

47. Kahn, R. L.; McDermott, E. B., and Marcus, S.: Effect of Temperature on Kahn Reaction, with Serologically Negative Sera in Absence of Syphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **25**:173 (March) 1941.

the last-named group behaves in the same manner as the serum of lower animals.

#### PUBLIC HEALTH ASPECTS

*Syphilis and National Defense.*—As in previous wars, so now does venereal disease rank high among the causes for lost manpower in the armed forces and in industry.

Young,<sup>48</sup> who was in charge of venereal diseases in the American Expeditionary Force during the last war, described the difficulties which were encountered in the control and treatment of these diseases in the American, British and French armies. He ascribes the eventual reduction in the incidence of venereal diseases in the American Expeditionary Force to the foresight and interest of General John J. Pershing, though much of the credit should go to Young himself and to the organized group of some 250 venereal disease control officers built up under his direction.

Parran and Vonderlehr<sup>5</sup> are most anxious that venereal disease be properly controlled during the present national emergency. They are interested not only in the loss of man hours in the armed forces but in the possible loss of the gain already made in the control of venereal disease in the civilian population. We quote from their book "Plain Words About Venereal Disease":

. . . Venereal disease remains the major cause of noneffectiveness among all the armed forces. In 1940, the Surgeon General of the Army reported days lost from duty because of syphilis and gonorrhea to be greater than from any other cause. He added that time-wasting diseases had changed little in order of importance during the last five years. In the Navy, venereal disease took second place among all causes of sickness but was responsible for the most days lost from duty.

Of the first million men examined by Selective Service, almost 60,000 were rejected because they showed evidence of venereal disease. The new army is going into the ranks clean of infection. But unless our high command takes the job of control more seriously than up to now, their extreme care in selection will be wasted. Data from the nine corps areas show the disease rate steadily rising from infection acquired in the Service. Of almost equal concern to all citizens is the fact that to date the special plans for medical rehabilitation of rejects turned back by the draft have not been put into action. . .

. . . Why should this proud young army, the cream of our youth, be allowed to contract venereal disease just because all armies have been torn by it in the past?

Yet this is happening now in the mobilization areas. It is equally true in the boom towns where the defense industries have turned villages into cities overnight. The good work begun in national control will be canceled, the declining attack rate of syphilis and gonorrhea will be swiftly reversed, unless to

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48. Young, H.: A Surgeon's Autobiography, New York, Harcourt, Brace & Company, Inc., 1940.



our concern with munitions and maneuvers and equipment we add specific attention to the protection of our men in the armed forces and in the factories which supply them. . . .

Thanks to the efficiency of the Medical Corps in stressing prophylaxis and adapting many—though not all—of the modern improvements in treatment, the venereal disease rate in the army up to September, 1939, when the total strength was less than 200,000 men, averaged 14 per thousand for syphilis and 27.7 for gonorrhea—far less than in the regular army before the declaration of war against Germany in 1917; but far more than the present prevalence in our population outside the army.

Since September, 1939, the army has been multiplied more than eight times, increasing in total strength to almost 2,000,000 men; that is, for every man in the army two years ago, seven more volunteered or have come in through Selective Service, and every man of those seven was completely free from venereal disease. As has been pointed out earlier, every man was given a blood test for syphilis. If it was positive, another test was made to obviate the least chance of a laboratory error. If that, too, was positive, he was summarily rejected for army service. This was without regard for the unanimous recommendation of the syphilis experts of the United States, which was that unless a man otherwise eligible showed the destructive effects of late syphilis, it would be better to accept him and treat him—for with proper treatment a man with early syphilis is neither dangerous to his associates nor incapacitated for duty—than to throw him back upon the community untreated. . . .

With a dilution of 7 men, uninfected, for each man in an army population of which 14 in every thousand already were reported infected with syphilis and slightly more than 27 per thousand with gonorrhea, one would have expected a swift and permanent flattening of the army rates of infection. What has happened?

In reports now at hand from the several corps areas, a reduction in venereal disease rates was noticeable for a few weeks after each detachment of fresh men poured into the ranks. Then steadily, inevitably, in regiment by regiment the rates crept up. By March, 1940, for example, the over-all syphilis rates were back to 11.3 per thousand; the 1939 mark was exceeded by the rate of 35.9 for gonorrhea. With a new influx of men, the June, 1941 syphilis rates were down again to 8.1 per thousand. Either the devices for detecting gonorrhea in selectees were not effective or new infections occur swiftly and in large numbers immediately after inclusion of the volunteers and selectees; for there has been practically no decline in the gonorrhea rate of the army during the periods when the largest numbers of presumably uninfected men were added. The trend has been steadily higher through 1940 and to the end of June, 1941, when 40.3 gonorrhea infections per thousand mean strength were admitted to medical treatment. . . .

Any doctor familiar with the problem will admire the concern of the Army to give its men good treatment once they are infected. He finds it difficult to understand the apparent lack of concern when it comes to preventing the infection, especially when it follows absolute refusal to take and treat men in the draft who would have made good soldiers.

The major role which commercialized prostitution plays in the infection of soldiers is pointed out, and the measures employed against prostitution in 1917-1919 are discussed. Referring to the present situation, Parran and Vonderlehr assert:

Prior to defense mobilization, the commercial prostitute was barely breaking even with amateur and part-time competition. Suddenly the situation has been

reversed. The vice rings saw a vast and profitable field of operation. The recruitment of prostitutes has kept pace with recruitment of the Army. It is one of our most expanded war industries.

The frame work for effective action against it is already in place. The action as yet has not been undertaken. Early in 1940, the War and Navy Departments, the Public Health Service, and the 48 state health departments entered into an official agreement for improving the control of venereal diseases in the areas where the armed forces or national defense employees were newly concentrated. In addition to agreeing upon scientific measures to be used in both the military and civilian population for early diagnosis, proper treatment, full interchange of reports on known cases and contacts, and quarantine of recalcitrant patients whose disease was in the communicable stage, these agencies agreed to co-operate with the local police in *repressing prostitution*. . . .

In July, 1941, a national policy regarding prostitution was authoritatively declared through passage of the May Act. Under the provisions of this Act, it is unlawful to engage in prostitution, to solicit for the purposes of prostitution, to aid and abet prostitution, to keep a house of ill fame, or *to rent or permit the use of a vehicle or building for that purpose* within such areas around military and naval establishments as the Secretaries of War and Navy may designate in order to protect the health and welfare of their forces. The Federal Bureau of Investigation is responsible for its enforcement.

The Secretaries of War and Navy and the Federal Security Administrator, to whom the Public Health Service reports, are directed to take necessary steps to prevent violation of the law, working with state and local authorities to carry out its purposes. Those found guilty of violations are subject to a fine of not more than \$1,000, or imprisonment for not more than one year, or both. . . .

The plan on paper is perfect. Nothing has been done. . . .

It would be better that the May Act had never been passed than to have it passed and lie fallow. Here and there was a state or city struggling to pull itself up by its own bootstraps, using the national interest as a lever to put pressure on its own law enforcement agencies, and waging guerrilla warfare upon commercialized prostitution. With the May Act passed, but no gesture to enforce it, the ordinary hard-headed citizen feels that the national interest in the problem is, at the best, ambiguous; the overlords of vice feel they have a green light at the crossroads, with no speed limit. . . .

Incidentally, Parran and Vonderlehr do not fail to emphasize again that regulation of prostitution is a completely inefficient public health measure and to show clearly that a policy of repression, requiring cooperation of the Army, the Navy, local law enforcement agencies and civilian public health authorities, is the only sound method of dealing with the problem.

These quotations and comments emphasize the authors' thesis that the Army is dilatory in venereal disease control as compared with its own effort in 1917-1919 or with the civilian effort, carried out under the fearless leadership of the authors themselves, since 1936. The civilian public health control program is too briefly described, but its magnitude and accomplishments are illustrated by statistical data.

Say Parran and Vonderlehr of the civilian effort:

After only three years' work—and most of the first year had to be spent tooling up—with one-tenth of the time elapsed, and having had available only

about one-quarter of the money considered necessary to do the job, it is heartening to report that the 1936 estimate on syphilis can be improved by one-third. If we hold our lines in the general population and extend our effort to clean up the infection accumulating in the mobilization areas, in 20 years syphilis can be made a rare disease.

The chances look even better for exterminating gonorrhea. If we attack the disease where we find it everywhere in the United States, employing the machinery already set up for syphilis control to use the brilliant new weapon, sulfathiazol, gonorrhea should become a rare disease in a single decade.

The book is a report of great progress made in five years and a strong and urgent incentive to further specialized effort by the Army, the Navy, civilian authorities and the people themselves, lest the gain of these years be lost by the circumstances created by the national emergency.

Moore<sup>49</sup> discusses the problem of venereal disease and national defense and particularly emphasizes the need of specially trained officers in the Army, the Navy and the Public Health Service. He summarizes:

The venereal diseases in the U. S. Army and Navy are still, as they always have been, a problem of the first magnitude. Except in the event of epidemics of other acute infectious diseases, they remain, as they always have remained, the major infectious disease problem which the services face. Their importance is increased, as always, under conditions of mobilization for training or for war. The high incidence of venereal disease is of military importance because of loss of manpower, of civilian public health importance because of the additional spread of these diseases to the civilian community by infected military and naval personnel, both during and after their period of service; of individual importance because of the disabilities produced by these diseases, especially syphilis, and of importance to the taxpayers because of the cost of treatment of infected personnel and of compensation for subsequent disability.

It is believed that the control of these diseases in the Army and Navy depends in the first instance on the creation of a group of medical officers with special training in clinical and public health control measures, who devote full time to their particular task, and of the direction of these officers in the application of these measures by the newly created subdivisions of venereal disease control, now established in the offices of the respective Surgeon Generals. Given this, the job can be well done. Failing this, it will be half done. Let's get on with it!

The problem in the Navy is summarized by Stephenson.<sup>50</sup> In normal times, the paths of the naval medical officer and the civilian physician or health officer seldom cross. In this emergency, however, in which the nation must bring about in the shortest possible time a great increase in armed forces, the most intimate cooperation between service officers and civilian physicians will be necessary to control epidemic diseases of all types. In this regard the venereal diseases are particularly important

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49. Moore, J. E.: Venereal Diseases and National Defense, *J. A. M. A.* **117**: 255 (July 26) 1941.

50. Stephenson, C. S.: The Naval Medical Officer's Public Health Activity, *South. M. J.* **34**:90 (Jan.) 1941.

because of their controllability, their high incidence and the necessity for control measures which involve the closest cooperation between service and civilian officials.

During World War I, and in spite of the fact that the American armed forces attained a low rate for the venereal diseases, the Army, Navy and Marine Corps combined had 157,146 more new cases of venereal disease than there were wounds in battle and the armed forces lost 7,492,410 sick days, or the equivalent of nearly 20,600 men absent from service for a whole year. Expressed in terms of ship complement, there were enough days lost to man five aircraft carriers and nine World War type destroyers. Since this huge morbidity is largely preventable, Stephenson examines some of the methods of approaching it in the present emergency. He concerns himself particularly with prostitution, which he asserts must be repressed as a purely public health measure. Prophylaxis is also capable of protecting exposed personnel if applied properly and within the proper period of time.

Stephenson agrees further that Army and Navy regulations which penalize men for the contraction of venereal disease largely defeat their own purpose, because of the natural tendency so stimulated to concealment on the part of infected personnel.

*Progress in Syphilis Control in the Southern States.*—Heller<sup>51</sup> summarizes the progress in syphilis control in the southern states as follows:

Advances in syphilis control have been made during the period 1935-1939 in the Southern states where the problem admittedly is the greatest. Funds derived from the provisions of Title VI of the Social Security Act and the LaFollette-Bulwinkle Bill have enabled marked expansion to take place in venereal disease control programs throughout the area. A good start has been made and there is every reason to believe that control of syphilis will continue to go forward. A few of the outstanding accomplishments are listed:

1. All the Southern states have either a separate division or a subdivision of venereal disease control in the state health department. In June, 1935, only four of the seventeen had such administrative organization.
2. Twelve of the seventeen states in June, 1939, had one or more full-time venereal disease control officers in comparison with two in June, 1935.
3. All Southern states engage in the free distribution of drugs for the treatment of syphilis to indigent venereally infected individuals. Four states distribute drugs for the treatment of all. In 1935 only nine states distributed drugs for indigents and only one, Maryland, for all.
4. Serodiagnostic tests for syphilis are free in all of the Southern states and have been improved as a result of the serologic evaluation studies. Equipment for the darkfield diagnosis of early syphilis is more freely available than formerly, but is not yet utilized satisfactorily.

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51. Heller, J. R., Jr.: Progress in Syphilis Control in the Southern States, South. M. J. 33:681 (July) 1940.

5. There has been an increase in the number of syphilis cases reported to state health departments by 162.3 per cent during the past four years.

6. There has been an increase in the number of clinics for the treatment of venereal diseases from 285 in 1934 to 1,351 in 1939.

7. Epidemiologic investigation of early and some other cases of syphilis is performed to some extent in all states. The efficiency and value of these investigative procedures have been well demonstrated by a number of health departments during the last four years. Clinics generally, however, do not take advantage of this practice of case finding to the greatest extent.

8. All Southern states have either allotted or appropriated directly state funds for the control of venereal diseases. Most states and local governments have not yet appropriated enough funds to operate properly an adequate control program.

9. Educational programs have been projected in every state. A favorable public sentiment toward the problem of venereal disease is believed to exist, though this should be cautiously sustained by skilful methods of approach to the public consciousness.

*Syphilis in Industry.*—After intimate experience with the syphilis control program in Buffalo and the particular technic of its application in various industries, Osborne and his colleagues<sup>52</sup> conclude:

The incidence of syphilis among industrial employees in a large northern industrial city . . ., excluding the Negro employees, . . . is now approximately 4 per cent.

The kind or type of syphilis to be expected in different employee groups is of importance. Early syphilis is a minor hazard except among large groups of employees 30 years of age and younger. . . Late cardiovascular and neurosyphilis are the greatest hazards to industry, to the public, and to the employee. . . Late neurosyphilis is of greatest importance among clerks, skilled workers, and railroad employees.

The danger of infection from food handlers, clerks, barbers, etc., has been greatly overrated. More attention should be paid to infections transmitted in the usual way among mixed social groups from within and outside the plant.

The proper syphilis program in an industrial plant will prevent the frequently serious and expensive complication of syphilis and trauma.

Suggestions for improving the syphilis program in industry for the executives and for industrial physicians and surgeons can largely be expressed with the one word "education." With this in mind we have made definite concrete suggestions for executives and industrial physicians and surgeons which we think should be of distinct benefit in encouraging the adoption of a proper syphilis program in industry. . .

Cormia<sup>53</sup> points out that syphilis is a community liability comparable to tuberculosis. He estimates the cost of caring for syphilitic patients in Montreal, Canada, at an annual minimum of \$355,000.

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52. Osborne, E. D.; Traenkle, H. L., and Dolce, F. A.: *Syphilis in Industry*, New York State J. Med. **40**:1362 (Sept. 15) 1940.

53. Cormia, F. E.: *Direct Cost of Syphilis to City of Montreal*, Canad. M. A. J. **43**:278 (Sept.) 1940.

## DRUGS

*Acetylglycarsenobenzene (Solusalvarsan).*—Guy and his co-workers<sup>54</sup> and Hahn<sup>55</sup> have treated sizable groups of patients with early syphilis with acetylglycarsenobenzene (solusalvarsan). The drug proved to be therapeutically effective, but the incidence of major treatment reactions was sufficiently high to preclude its further use.

*Azoarsenobenzene.*—Friedheim<sup>56</sup> describes in some detail the results obtained in the treatment of 40 patients with early syphilis with a new arsenic compound which he calls azoarsenobenzene 4197. In addition, briefer consideration is given to the use of the substance in the treatment of patients with other forms of syphilis and with African sleeping sickness.

The drug is the sodium salt of 4,4'-dihydroxyarsenobenzene-3,3' bis [(azo-2)naphthol-(1) disulfonide 4,8], which is described as having a constitution of an acid azo dye. It can be prepared in pure crystalline form. Both the dry substance and its aqueous solution are of great stability in the presence of oxygen. It is said to be diffusible and to penetrate readily into the cerebrospinal fluid.

In the 41 cases of African sleeping sickness (among which were 4 in which other forms of arsenotherapy had failed) and in 40 cases of primary secondary syphilis the preparation proved to have powerful trypanocidal and spirocheticidal activity.

*Aldarsone.*—Little clinical attention has been given to aldarson, a pentavalent arsenical the chemical constitution of which corresponds probably to the formula of sodium methylenesulfonaminohydroxyphenyl-arsonate, in spite of the fact that it was discovered more than seven years ago. Spiegel and Liefer<sup>57</sup> have studied this drug clinically. One hundred and thirty-three patients were given a total of 6,702 injections of aldarson. All varieties of syphilis of the central nervous system were encountered in this group. The authors conclude as follows:

Aldarsone, a pentavalent arsenical, proved to be effective in the treatment of neurosyphilis, especially in the meningovascular type. Improvement was noted

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54. Guy, W. H.; Goldmann, B. A.; Gannon, G. P., and Slone, J.: Acetylglycarsenobenzene (Arsphenamine Derivative) in the Treatment of Syphilis: Preliminary Report, *Arch. Dermat. & Syph.* **42**:1046 (Dec.) 1940.

55. Hahn, R. D.: Solusalvarsan (3,4'-Diacetylamino-4-Hydroxyarsenobenzene-2'-Sodium Glycolate) in the Treatment of Early Syphilis, with Some Observations on the Rate of Fall of Serum Reagin, *Am. J. Syph., Gonorr. & Ven. Dis.* **25**:628 (Sept.) 1941.

56. Friedheim, E. A. H.: Contribución a la quimioterapia por los arsenicales orgánicos. El azo-arsenobenzole en el tratamiento de la sífilis y de la enfermedad del sueño africana, *Rev. argent. dermatosif.* **25**:66, 1941.

57. Spiegel, L., and Liefer, W.: Treatment of Neurosyphilis with a New Pentavalent Arsenical, Aldarsone, *Am. J. Syph., Gonorr. & Ven. Dis.* **25**:472 (July) 1941.

in the various spinal fluid tests, and also in the blood Wassermann reaction. In syphilitic optic atrophy, there was no contraindication to the use of aldarson. In fact, visual fields showed improvement, and there was no deterioration of vision, such as sometimes follows tryparsamide. Gain in weight and general well-being was observed in many instances. A great majority of patients improved and were able to resume their previous occupations. There were very few relapses. Untoward reactions occurred rarely and were of a mild character. No immediate reactions were observed and only one fixed skin eruption was noted. Aldarson may be used continuously over a long period of time, some patients having received over a hundred injections at frequent intervals.

For the present, however, and until these favorable results are more widely confirmed, the use of aldarson should be regarded as still in the experimental stage.

*Experimental Study of Arsenical Compounds.*—Kolmer, Brown and Rule<sup>58</sup> have attempted a study of the therapeutic activity of arsphenamine, neoarsphenamine, sulfarsphenamine and bismarsen in the treatment of rabbit syphilis in relation to the urinary excretion of arsenic. They found, insofar as arsphenamine and neoarsphenamine are concerned, that for single injections to result in biologic cure of acute testicular syphilis in rabbits the dose should be sufficient to yield at least 0.15 to 0.38 mg. of arsenic in the total daily output of urine for the first three days.

Eagle<sup>59</sup> describes the methods which he uses to assay (1) the treponemicidal activity in vitro of a series of substituted phenylarsenoxides, (2) their therapeutic activity in syphilitic rabbits and (3) their toxicity in white mice and rabbits.

Eagle and his co-workers<sup>60</sup> studied 27 monosubstituted phenylarsenoxides from the point of view of toxicity in mice and rabbits, treponemicidal activity in vitro and therapeutic activity in syphilitic rabbits. The ratio of relative treponemicidal activity in vitro to relative mouse toxicity varied from 0.68 to 4.0, as compared with an arbitrary standard of 1 for unsubstituted phenylarsenoxide. Since the corresponding value for mapharsen was 6.0, none of the twenty-seven derivatives examined is potentially as valuable as mapharsen in the

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58. Kolmer, J. A.; Brown, H., and Rule, A. M.: The Therapeutic Activity of the Organic Arsenical Compounds in Syphilis of Rabbits in Relation to the Urinary Excretion of Arsenic, *Am. J. Syph., Gonorr. & Ven. Dis.* **25**:486 (July) 1941.

59. Eagle, H.: The Toxicity, Treponemicidal Activity, and Potential Therapeutic Utility of Substituted Phenylarsenoxides: I. Methods of Assay, *J. Pharmacol. & Exper. Therap.* **69**:342 (Aug.) 1940.

60. Eagle, H.; Doak, G. O.; Hogan, R. B., and Steinman, H. G.: Toxicity, Treponemicidal Activity and Potential Therapeutic Utility of Substituted Phenylarsenoxides: Monosubstituted Phenylarsenoxides (Cl; NO<sub>2</sub>; CH<sub>3</sub>; C<sub>2</sub>H<sub>5</sub>OH; C(CH<sub>3</sub>)<sub>3</sub>; NOH; NH<sub>2</sub>; OH, CH<sub>2</sub>NH<sub>2</sub> and Derivatives), *J. Pharmacol. & Exper. Therap.* **70**:211 (Oct.) 1940.

treatment of syphilis. This was confirmed for seven of these compounds by the assay of therapeutic activity and toxicity in syphilitic rabbits.

Further study of monosubstituted phenylarsenoxides (sixteen additional compounds) <sup>61</sup> revealed regular inhibition of the treponemicidal activity of phenylarsenoxide by acidic substituents and suppression of this inhibitory effect when the acidic group was blocked, as by esterification. None of the arsenoxides discussed in this paper appears to be of potential utility in the treatment of syphilis.

*Sobisminol*.—From the results of experiments on 49 rabbits which drank sobisminol solution, varying in strength from 0.025 to 0.6 per cent, Hanzlik and his co-workers <sup>62</sup> conclude that it is possible in this manner to protect these animals from experimental syphilis. The critical concentration of the drug in solution was 0.4 per cent. The authors suggest a tentative schedule for the prophylaxis of human syphilis by the oral use of sobisminol capsules.

Hanzlik and van Winkle <sup>63</sup> have further studied the oral administration of sobisminol solution. They found that either after voluntary drinking of sobisminol solution or after its direct gastric administration there were definite spirocheticidal effects and promotion of healing of local lesions in rabbit syphilis.

Kolmer, Brown and Rule <sup>64</sup> have studied in experimental rabbit syphilis the therapeutic effectiveness of sobisminol solution, which contains about 20 mg. of elemental bismuth per cubic centimeter, and water-soluble bismuth and potassium tartrate, which contains about 64 per cent elemental bismuth. An adequate number of rabbits infected with the Nichols-Hough strain of *S. pallida* were used in the experiments. The authors found that either drug, administered orally over a period of twenty days or by single intramuscular injections, was about as therapeutically effective as the other in terms of elemental bismuth and likewise in terms of urinary excretion of bismuth.

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61. Eagle, H.; Hogan, R. B.; Doak, G. O., and Steinman, H. G.: Toxicity, Treponemicidal Activity and Potential Therapeutic Utility of Substituted Phenylarsenoxides: Monosubstituted Compounds; Acids, Esters, Benzophenone, Methylsulfone, *J. Pharmacol. & Exper. Therap.* **70**:221 (Oct.) 1940.

62. Hanzlik, P. J.; Lehman, A. J., and van Winkle, W., Jr.: Protective Value of Bismuth in Syphilis: Experimental Results with Drinking of Sobisminol, *Am. J. Syph., Gonorr. & Ven. Dis.* **24**:468 (July) 1940.

63. Hanzlik, P. J., and van Winkle, W., Jr.: Effects of Sobisminol Solution Orally in Experimental Syphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **25**:508 (July) 1941.

64. Kolmer, J. A.; Brown, H., and Rule, A. M.: Sobisminol Solution and Water-Soluble Potassium Bismuth Tartrate by Oral and Intramuscular Administration in the Treatment of Experimental Rabbit Syphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **25**:595 (Sept.) 1941.



*Bismuth Compounds.*—Kolmer and others<sup>65</sup> present a detailed analysis of the relation between the urinary excretion of four bismuth compounds, of which two are water soluble (bismuth and potassium tartrate and thio-bismol) and 2 are water insoluble (bismuth subsalicylate and bismuth oleate), and their prophylactic and therapeutic activity in rabbit syphilis. They conclude that to effect biologic cure of acute testicular syphilis of rabbits, the dose of any of these compounds must be such as to yield at least 0.3 mg. of bismuth in the total daily output of urine for a period of fourteen to seventy-five days. This excretion level may vary with the chemical constitution of the compound. A constantly sustained level of urinary excretion was found to be more efficacious than a fluctuating level.

A study was made by Thurmon and Benotti<sup>66</sup> of the daily excretion of bismuth in the urine of 9 patients after the administration of clinical doses of an oil-soluble bismuth compound (bismuth ethylcamphorate). The 2 cc. doses (80 mg. of elemental bismuth) administered at seven day intervals appeared to be adequate to maintain a sustained circulation of bismuth over a sufficient period to fall within the accepted standards of therapeutic effectiveness.

Kolmer and his co-workers<sup>67</sup> tested six water-soluble bismuth compounds for their immobilizing effects in vitro on *S. pallida* obtained from rabbit testicular syphilomas. They conclude that immobilization is due to true treponemicidal effects but that the in vitro test is too inaccurate for acceptance as a measure of therapeutic effectiveness, since there is no correlation between the effective in vitro and in vivo doses. Culture spirochetes and *Trypanosoma equiperdum* required higher concentration for immobilization than did *S. pallidum*.

*Mobilization of Bismuth by Ammonium Chloride.*—Corson and his collaborators<sup>68</sup> selected for study patients (1) who had received not less than forty injections of bismuth subsalicylate, averaging 10 mg. each, (2) whose last injection had been received from four months to four years previous to the study and (3) in whom roentgenograms of the buttocks showed heavy deposits of bismuth. Utilizing the rapid method

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65. Kolmer, J. A.; Brown, H., and Rule, A. M.: Therapeutic Activity of Bismuth in Rabbits in Relation to Its Urinary Excretion, *Am. J. Syph., Gonorr. & Ven. Dis.* **24**:415 (July) 1940.

66. Thurmon, F. M., and Benotti, N.: Excretion of Bismuth in Urine of Patients Treated with Bismuth Ethyl Camphorate, *Arch. Dermat. & Syph.* **42**: 1073 (Dec.) 1940.

67. Kolmer, J. A.; Kast, C. C., and Rule, A. M.: Spirocheticidal and Mechanism of Activity of Bismuth Compounds in Vitro and in Vivo in Relation to Therapeutic Effectiveness, *Am. J. Syph., Gonorr. & Ven. Dis.* **24**:439 (July) 1940.

68. Corson, E. F.; Decker, H. B., and Williams, T. L.: Mobilization of Bismuth Produced by Ammonium Chloride, *Arch. Dermat. & Syph.* **42**:868 (Nov.) 1940.

of Hanzlik, Lehman, Richardson and van Winkle, the authors tested the urine of each patient on two occasions, with negative results in all but one examination. Eight patients were then treated with 30 to 40 grains (1.94 to 2.59 Gm.) of ammonium chloride in compound elixir of pepsin N. F. daily; a ninth was given the compound elixir alone. The reaction of the urine to tests for bismuth became positive, usually slightly so, in the treated patients and remained negative in the control.

#### UNTOWARD EFFECTS OF TREATMENT

*Aplastic Anemia.*—Although fortunately rare, aplastic anemia due to the administration of arsphenamine is a well known complication of the use of this type of medication. In spite of the recent and growing popularity of mapharsen, however, only 1 case of aplastic anemia apparently resulting from the use of this drug had been reported previous to the 2 cases recorded by Kirkham and Perlmutter<sup>69</sup> and Creswell and Roth.<sup>70</sup>

*Granulocytopenia.*—A case of granulocytopenia following medication with neoarsphenamine is described in detail by Epstein and Falconer.<sup>71</sup> The patient tolerated mapharsen, without a reaction. A preliminary report based on 30 patients who had no treatment reactions suggests that neoarsphenamine usually causes a diminution in the leukocytes and platelets of the peripheral blood and that mapharsen is much less likely to produce these changes.

*Thrombopenic Purpura.*—Falconer and his collaborators<sup>72</sup> have for years been following a group of 7 patients, in 6 of whom thrombopenic purpura developed after the administration of neoarsphenamine; in the seventh the causative drug was bismarsen. In all cases, after the original spontaneous attack, the reaction had been experimentally reproduced several times. As to the effect of vitamin C on this reaction, the authors state:

Vitamin C in crystalline form as ascorbic acid, administered parenterally, orally and ingested in the diet, was given in varying amounts to these 7 patients,

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69. Kirkham, D., and Perlmutter, M.: Fatal Aplastic Anemia Following the Use of Mapharsen: Report of Case, *Arch. Dermat. & Syph.* **43**:111 (Jan.) 1941.

70. Creswell, G. W., and Roth, G. B.: Further Experiences with Mapharsen in Syphilis: Report of Fatality, *M. Ann. District of Columbia* **10**:230 (June) 1941.

71. Epstein, N. N., and Falconer, E. H.: Effects of Neoarsphenamine and Mapharsen (Arsenic Preparation) on Formed Elements of Blood: Granulocytopenia Following Neoarsphenamine Therapy in Patient Who Subsequently Received Mapharsen Without Untoward Reaction, *Arch. Dermat. & Syph.* **42**:909 (Nov.) 1940.

72. Falconer, E. H.; Epstein, N. N., and Mills, E. S.: Purpura Haemorrhagica Due to the Arsphenamines: Sensitivity in Patients as Influenced by Vitamin C Therapy, *Arch. Int. Med.* **66**:319 (Aug.) 1940.

to determine whether it modified their sensitivity to the arsenicals or inhibited the occurrence of thrombopenic purpura following the administration of the arsenical responsible for their sensitivity. . . . At no time and in no patient observed was there any appreciable modification of sensitivity reaction during or after administration of vitamin C.

*Erythema of the Ninth Day.*—In a comprehensive article on erythema of the ninth day, Peters<sup>73</sup> reviews the literature on the subject and analyzes completely 54 additional cases. The author summarizes the material as follows:

1. Fifty-four patients with the ninth-day erythema of Milian syndrome are reported. Fifty-two had dermatologic manifestations and two had no cutaneous involvement.

2. Fifty-two patients had syphilis. Sixty-three per cent were in the early infectious stages and 36 per cent had either late, late latent, or congenital syphilis.

3. The ages of these patients ranged from 8 to 52 years. The ratio of males to females was 1:2. The ratio of whites to colored was 1.7:1.

4. The drugs producing E9 [erythema of the ninth day] were arsphenamine, neoarsphenamine, mapharsen and acetylglycarsenobenzene. No correlation between the size of the dose and the occurrence of E9 could be found. Fifty-two patients had two or more injections of the drugs prior to E9.

5. The majority of patients were acutely ill. The usual symptomatology consisted of a prodrome occurring abruptly between the fifth and the nineteenth days (average 7.8 days) after the first arsenical injection and manifested by malaise, chills, fever, anorexia, nausea, vomiting, generalized aches, headache, and sore throat. This was followed one day later by the appearance of a generalized rash variously described as morbilliform, scarlatiniform, blotchy or macular erythematous, erythema multiforme-like and rarely urticarial. The eruption appeared between the seventh and twentieth days after the first injection (average ninth) and lasted from less than twenty-four hours to as long as twelve days (average five days). Branny desquamation occurred in two patients. Examination revealed that over 70 per cent of the patients had general lymph node enlargement, enlarged palpable cervical nodes and tonsillar hypertrophy; some had conjunctival suffusion. Hepatomegaly was noted in 9 patients (16.6 per cent), jaundice in 7 patients (13 per cent), and splenomegaly in 3 patients (5.5 per cent). The average duration of the syndrome was six days, five days of the duration of the erythema and one day for the prodrome. There were no fatalities.

The immediate associated reactions, integral features of the syndrome, were mainly visceral and occurred in 24 per cent of this series. These consisted of 8 patients with "hepatitis," 4 with hepatomegaly alone, 2 with nephritis, and 1 each with splenomegaly alone and granulocytopenia.

7. Delayed complications, caused by further treatment with the arsphenamine drugs, occurred in 53 per cent of 36 patients and consisted of dermatitis (all types), recurrent E9, nitritoid reactions, fever, gastrointestinal reactions, and intolerance to the usual trivalent arsenicals.

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<sup>73</sup>Peters, E. E.: The Syndrome of Milian's Erythema of the Ninth Day: Report of Fifty-Four Cases, *Am. J. Syph., Gonorr. & Ven. Dis.* **25**:527 (Sept.) 1941.

8. Seventy per cent of all patients receiving further arsenical preparations had reactions.

9. Of 15 patients who had reactions to the arsenical drugs prior to E9, 60 per cent developed serious sequelae to treatment after E9.

10. In general, the blood smears showed a shift to the left, and in severe cases there was a mild leucopenia of the granulocytic series with a relative monocytosis or lymphocytosis.

11. Forty-four per cent of the patients had eosinophilia of 5 per cent or greater. Of this group 87.5 per cent had serious immediate manifestations or subsequent treatment complications while of the patients with eosinophilia of 0 to 4 per cent only 35 per cent had reactions. The higher the eosinophilia the greater the likelihood of serious immediate or delayed complications.

12. Of the patients who received further arsenotherapy during or within two weeks from the onset of the prodrome, 77 per cent had serious complications, while of those who received treatment later than two weeks only 28 per cent had complications and these were relatively mild.

13. There were two instances of infectious relapse of the syphilitic disease in this series.

Hanger and Gutman<sup>74</sup> report 12 cases of postarsphenamine jaundice apparently due to obstruction of the intrahepatic biliary tract. This form of hepatitis is apparently closely related to erythema of the ninth day. Biopsy of the liver in 4 cases showed absence of parenchymal degeneration, pericholangitis and bile thrombi in the finer biliary radicles. The onset of reaction in all cases occurred after the second or third injection of an arsenical and was accompanied by constitutional and gastrointestinal symptoms. A transitory erythema was noted in 6 cases. Jaundice appeared several days later and persisted for weeks or months. The cutaneous eruptions as well as the time of onset suggest the relation to erythema of the ninth day. There were no deaths. Chemical studies of the blood yielded elevated values for phosphatase and cholesterol, and the cephalin flocculation reaction was negative. These findings were similar to those recorded for patients with other types of obstructive jaundice. The mechanism producing jaundice associated with erythema of the ninth day is therefore apparently different from the more commonly observed jaundice resulting from the administration of an arsenical, which is thought to be due to mild toxic hepatitis and is not of the obstructive type.

Thomas and Cañizares<sup>75</sup> report briefly and in detail, respectively, the cases of 2 patients whose original reaction to the arsenical drugs seems from the description typical of erythema of the ninth day. One patient had received mapharsen and the other neoarsphenamine, and in the case

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74. Hanger, F. M., Jr., and Gutman, A. B.: Postarsphenamine Jaundice Apparently Due to Obstruction of Intrahepatic Biliary Tract, *J. A. M. A.* **115**: 263 (July 27) 1940.

75. Thomas, E. W., and Cañizares, O.: Relapsing Early Acute Arsenical Erythema: Report of Two Cases, *Arch. Dermat. & Syph.* **42**:30 (July) 1940.

of each the attempt to resume the same drug immediately after the erythema had faded was followed by a recurrence of fever, constitutional symptoms, erythema and sore throat. In 1 case the relapse was repeated, but both patients eventually were able to tolerate well the drug to which they originally had reacted.

Alessi <sup>76</sup> reports a case in which erythema of the ninth day was associated with neurologic manifestations consisting of cerebellar ataxia, paraplegia and dysarthria.

*Arsenical Dermatitis.*—Cormia,<sup>77</sup> in a discussion of the possible etiologic considerations in postarsphenamine dermatitis, considers the role of initial intradermal injection of the drug, local tissue injury, variation in drug lot, prior contact or seborrheic dermatitis, focal or cutaneous infection, hypovitaminosis C, capillary damage and hepatic damage. He concludes, however, that the exact mechanism of cutaneous sensitization to arsphenamine and the relative importance of these various possible contributory factors remain unknown.

Cormia,<sup>78</sup> working with guinea pigs, was unable to produce either epidermal sensitivity or anaphylaxis by the administration of mapharsen. Neutralized arsphenamine readily produced cutaneous sensitization but not anaphylaxis, whereas a mixture of neutralized arsphenamine and homologous serum failed to produce cutaneous sensitization but did produce anaphylaxis. In these experiments it was thus possible to separate cutaneous and anaphylactoid reactivity by the use of a simple sensitizing antigen, on the one hand, and a conjugate arsphenamine antigen, on the other.

Frei <sup>79</sup> attempted specific cutaneous sensitization of guinea pigs to quinine, acetylsalicylic acid and barbital, with and without preceding or concomitant cutaneous sensitization to arsphenamine. The results were uniformly negative.

Olin <sup>80</sup> presents an interesting but somewhat incomplete report of his experiences in performing an intradermal test with neoarsphenamine on

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76. Alessi, D.: Encefalite arsenobenzolica con esantema del nono giorno. Lesione pontina definitiva, *Minerva med.* **1**:445 (May 26) 1940.

77. Cormia, F. E.: Etiologic Considerations in Postarsphenamine Dermatitis, *Am. J. Syph., Gonorr. & Ven. Dis.* **25**:189 (March) 1941.

78. Cormia, F. E.: Cutaneous Sensitization to Arsphenamine: Attempts to Induce Anaphylactic State with Different Arsphenamines: Production with Conjugate Arsphenamine Antigen, and Incidental Relation Between Anaphylactic and Cutaneous Hypersensitivity, *Arch. Dermat. & Syph.* **43**:103 (Jan.) 1941.

79. Frei, W.: Further Studies in Arsphenamine Hypersensitiveness in Guinea Pigs: II. Attempts at Experimental Specific Sensitization of Guinea Pigs to Quinine, to Acetyl Salicylic Acid, and to Barbital, With and Without Preceding or Concomitant Arsphenamine Sensitization, *J. Invest. Dermat.* **4**:111 (April) 1941.

80. Olin, T. E.: Sur l'intradermo-réaction comme critérium de l'intolérance à l'égard du salvarsan, *Acta dermat.-venereol.* **22**:176 (March) 1941.

70 women with syphilis. Some of these had previously exhibited some form of cutaneous reaction to antisyphilitic treatment, and others had not; the exact number in each group is not clear from the report. The test was performed by the injection of 0.1 cc. of a 10 per cent solution of neoarsphenamine into the skin of the forearm, and the results were read after forty-eight hours. In 63 of these 70 patients no reaction was observed. As treatment was carried out after the intracutaneous testing, erythema of the ninth day developed in 2 patients who had given negative reactions, but both of them tolerated further treatment with neoarsphenamine without event; however, exfoliative dermatitis developed in 2 other patients who had given negative reactions, and they were found to be permanently intolerant of treatment with an arsphenamine. The remainder of the patients (including 3 with strongly or slightly positive reactions) bore subsequent treatment with an arsphenamine without event. The author concludes, therefore, that intracutaneous testing is valueless as an index either of the presence or of the absence of actual or potential intolerance to the intravenous injection of an arsphenamine.

Chargin and Leifer<sup>81</sup> report 69 instances of fixed eruption in patients receiving trivalent arsenicals. There was 1 instance of double sensitivity to arsenicals and phenolphthalein. Race was a predisposing factor, since 79 per cent of the reactions occurred in Negroes. Lesions were most common on the face. The oral mucous membrane was involved in 2 cases. Lesions produced by one trivalent drug were usually activated by other trivalent drugs. In many cases activation was produced by acetarsone but never by tryparsamide. Patch tests were always negative. In spite of continued arsenotherapy no case of exfoliative dermatitis was observed.

From a review of the literature, Franks and Fisher<sup>82</sup> were able to find only 3 cases of sensitivity to both trivalent and pentavalent arsenicals. To these they are able to add the detailed reports of 2 additional cases.

Summarizing the 17 previously reported cases in which patients had been given mapharsen after recovery from dermatitis caused by other arsenical compounds, in most instances neoarsphenamine, Schoch and his collaborators<sup>83</sup> found that "after recovery from severe exfoliative dermatitis, 1 patient tolerated mapharsen and 10 did not; after recovery from mild arsphenamine dermatitis 5 patients tolerated mapharsen and

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81. Chargin, L., and Leifer, W.: Fixed Eruptions Due to Arsphenamines, *J. Invest. Dermat.* **3**:443 (Dec.) 1940.

82. Franks, A. G., and Fisher, S.: Sensitization to Arsenical Compounds: Sensitization to a Pentavalent Arsenical Following Use of a Trivalent Arsenical, *Arch. Dermat. & Syph.* **42**:808 (Nov.) 1940.

83. Schoch, A. G.; Alexander, L. J., and Long, W. E.: Mapharsen in Treatment of Forty Patients Following Arsphenamine Dermatitis, *Arch. Dermat. & Syph.* **42**:919 (Nov.) 1940.

1 did not." To these reports they add 40 more, concerning patients observed by themselves who after recovery from neoarsphenamine dermatitis were treated with small, gradually increasing doses of mapharsen. The 10 patients who had had exudative exfoliative dermatitis also exhibited cutaneous intolerance to mapharsen in doses of 5 mg. or less. Twenty-seven of the remaining 30 patients who had had eruptions of lesser severity tolerated mapharsen in full therapeutic doses. However, 14 of these patients did not have a recurrence of dermatitis when retested with neoarsphenamine.

Horne and Scarborough<sup>84</sup> determined capillary resistance by the negative pressure method in 10 patients with erythema or dermatitis occurring as a toxic manifestation of antisyphilitic therapy. All showed decreased capillary resistance (increased fragility). Vitamin P (hesperidin) was administered to 2 patients, with a resultant increase in capillary resistance.

*Postarsenical Jaundice.*—Gott<sup>85</sup> asserts that sufficient work has not been done on latent jaundice. He therefore has made bilirubin determinations before and after each course of antisyphilitic treatment on a large group of patients. He summarizes his results as follows:

A total of 1,000 bilirubin determinations were made on 679 syphilitic patients receiving regular treatment at the Louisville City Hospital Syphilis Clinic.

The incidence of bilirubin determinations which were 1.0 mg. per 100 cc. of serum, or above, was studied in relationship to the type of treatment, the stage of syphilis, and the age, race and sex of the patients.

As indicated by these tests, the incidence of latent jaundice in treated syphilitic patients did not show any conclusive variation from that found in the non-syphilitic and nontreated syphilitic control groups.

According to Horne,<sup>86</sup> the levulose tolerance test is of no value in detecting hepatic damage prior to the development of clinical signs, since in a large proportion of cases of postarsphenamine jaundice the results were within normal limits.

*Hemorrhagic Encephalitis.*—Rosahn<sup>87</sup> reports 2 cases of postarsenical hemorrhagic encephalitis, with autopsy observations. In the first case death supervened within a few hours after the inciting (tenth) injection and the examination of the brain showed only multiple intravascular

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84. Horne, G., and Scarborough, H.: Capillary Resistance in Toxic Manifestations of Antisyphilitic Therapy (Use of Vitamin P), *Lancet* 2:66 (July 20) 1940.

85. Gott, J. R., Jr.: The Incidence of Latent Jaundice During Antisyphilitic Treatment: An Analysis of Routine Bilirubin Studies, *Internat. Clin.* 4:181 (Dec.) 1940.

86. Horne, G. O.: Levulose Tolerance Test in Intolerance to Antisyphilitic Therapy, *Edinburgh M. J.* 47:801 (Dec.) 1940.

87. Rosahn, P. D.: Fatal Hemorrhagic Encephalitis Following Arsenical Treatment of Syphilis: Two Cases with Autopsy Findings, *Urol. & Cutan. Rev.* 44:488 (Aug.) 1940.

emboli, without perivascular hemorrhage or necrosis. In the second case the patient survived several days after the inciting (eleventh) injection, and in this instance necrosis and widespread hemorrhages were the dominant features. The author suggests that variability in duration of life is the essential factor in determination of severity of anatomic changes. Since the second patient had widespread purpura and neither clinical examination of the blood nor anatomic study of the bone marrow is reported, one wonders whether the gross hemorrhages in the brain may not have been purpuric in origin rather than due to true hemorrhagic encephalitis.

Levy<sup>88</sup> gives a clinicopathologic report of a case of hemorrhagic encephalopathy due to the administration of neoarsphenamine. In addition to the usual vascular necroses and perivascular hemorrhages, a severe meningeal inflammatory reaction and an intensive leukocytic and lymphocytic infiltration of the vessel walls and parenchyma are described. In view of the fact that the patient had early syphilis, with a positive Wassermann reaction of the cerebrospinal fluid, the possibility of coexistent syphilitic meningitis does not appear to have been entirely excluded.

*Substances Purported to Reduce the Toxicity of Arsenicals.*—Cormia<sup>89</sup> reports that 5 of 7 patients with previous arsphenamine dermatitis and with positive reactions to patch tests with neoarsphenamine were subsequently able to tolerate more of the same arsenical without reaction when massive doses of vitamin C were given. Attempted intradermal sensitization with neoarsphenamine of 13 patients with hypovitaminosis C was unsuccessful. Moreover, preliminary investigation of the vitamin C levels of the blood of 100 patients showed no significant variation between normal controls, syphilitic patients not receiving arsenic and those receiving arsenic, with or without reactions. The author feels that although vitamin C is related to arsphenamine sensitization, other, unevaluated factors may be necessary.

Farmer and his co-workers<sup>90</sup> noted a decline of the plasma level of ascorbic acid in patients receiving neoarsphenamine, even in the absence of a reaction. The occurrence of severe gastrointestinal reactions, drug fever, dermatitis and hepatitis necessitated the administration of exceedingly large doses of ascorbic acid to bring the plasma level to the optimal

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88. Levy, N. A.: Encephalopathy: Unusual Clinical and Histologic Observations, *Arch. Dermat. & Syph.* **42**:814 (Nov.) 1940.

89. Cormia, F. E.: Postarsphenamine Dermatitis: Relation of Vitamin C to Production of Arsphenamine Sensitiveness, and Its Use as Adjunct to Further Arsphenamine Therapy in Patients with Cutaneous Hypersensitiveness to Arsphenamines, *J. Invest. Dermat.* **4**:81 (Feb.) 1941.

90. Farmer, C. J.; Abt, A. F., and Aron, H. C. S.: Influence of Arsenicals, Bismuth and Iron on Plasma Ascorbic Acid Level, *Proc. Soc. Exper. Biol. & Med.* **44**:495 (June) 1940.



value (1.0 mg. per hundred cubic centimeters). Administration of ferrous sulfate also resulted in lowered plasma levels of ascorbic acid, while bismuth compounds were without effect. Data are not presented as to the number of patients studied or the incidence either of spontaneous or of drug-induced hypovitaminosis C.

Welcker<sup>91</sup> studied the urinary excretion of ascorbic acid by the so-called test dose or saturation method, utilizing as subjects 22 patients with intolerance to the arsenicals. He found no correlation between the degree of vitamin C saturation and the severity of reaction (mostly dermatitis). However, he did find daily intravenous injections of ascorbic acid to be beneficial in 8 patients with arsenical dermatitis. This is perhaps to be attributed to its strong reducing properties rather than to its role as a vitamin.

McDonald and Johnson<sup>92</sup> review the conflicting reports in the literature regarding the possibility of producing cutaneous sensitivity to neoarsphenamine by the intracutaneous injection of that drug, with particular reference to the role played by ascorbic acid. Some have claimed that this substance facilitates, others that it protects from, the development of sensitivity. These authors maintained guinea pigs on a scorbutogenic diet plus various doses of ascorbic acid. A group of animals on a diet completely free from vitamin C did not survive the period of the experiment; the other three groups exhibited average blood ascorbic acid levels of 0.33, 0.47 and 1.11 mg. per hundred cubic centimeters, respectively. In each of these three groups the median also closely approximated the mean.

No relation could be found in guinea pigs between the quantity of ascorbic acid administered parenterally (or the blood ascorbic acid level in the blood) and the sensitivity to repeated intradermal injections of 0.15 per cent neoarsphenamine.

MacKee and Astrachan<sup>93</sup> conclude, from a study of 107 patients, that liver extract is a useful therapeutic agent in the treatment of some patients suffering from manifestations of intolerance due to arsenicals, heavy metals or radiation; that it may prevent pruritis, gastrointestinal disturbances, nephritis, bone pain and erythema, and that it is a useful supportive measure in the treatment of patients with a history of previous intolerance or with "low resistance." The lack of a control series consisting of similar groups of patients not given liver extract and the

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91. Welcker, A.: *Salvarsanunverträglichkeit und Vitamin C*, *Klin. Wchnschr.* **19**:1281 (Dec. 14) 1940.

92. McDonald, F. M., and Johnson, H. H.: *Ascorbic Acid and Arsphenamine Dermatitis: An Experimental Study*, *Arch. Dermat. & Syph.* **43**:682 (April) 1941.

93. MacKee, G. M., and Astrachan, G. D.: *Value of Liver Extract in Cases Intolerant to Arsenicals, Heavy Metals and Radiation*, *J. Invest. Dermat.* **3**:409 (Oct.) 1940.

heterogenous nature and often minor character of the reactions cited do not permit the exclusion of the possibility that the results achieved might have been entirely fortuitous.

In an article entirely devoted to a critical review of the literature pertaining to the detoxifying effect of various substances (including those just considered) used in association with the arsphenamines, Doak<sup>94</sup> gives sixty-two references. He summarizes as follows:

The foregoing list of substances which have been suggested for admixture with the arsphenamines is by no means complete, since literally hundreds of compounds have been suggested. It is quite possible that some of these mixtures have merit. Any substance that reduces the toxicity and eliminates the unpleasant side reaction often produced by the arsphenamines, as claimed by various workers, would clearly merit extensive study. *To date, however, none of these mixtures has been subjected to the necessary experimental study.* Where animal experimentation has been done, it has often been performed on far too limited a series of animals to draw adequate conclusions. *The clinical results have been equally inconclusive.* An apparently favorable result in ten or fifteen patients does not warrant any generalization as to either therapeutic efficacy or toxicity. *It may safely be said, that, in spite of the hundreds of combinations that have been suggested, none has been conclusively shown to have any advantage over arsphenamine solutions alone.* [The italics are ours.]

*Reactions to Arsphenamine.*—Waugh and Milovich<sup>95</sup> analyze severe reactions to arsphenamine among 3,050 previously untreated patients with early syphilis who received a total of 34,780 injections. There were 2.44 severe reactions per thousand injections. The incidence tended to rise with increasing age. Dermatitis and icterus comprised 94 per cent of the total. Dermatitis occurred more than twice as frequently among women as among men, while icterus occurred one and one-half times as frequently among men as among women. Three deaths occurred, 1 from acute yellow atrophy of the liver and 2 from dermatitis.

*Reactions to Neoarsphenamine.*—Statistics compiled for the United States Navy<sup>96</sup> reveal that between 1925 and 1939, 1,301,913 injections of neoarsphenamine were administered, with 1 fatal reaction to each 26,570 injections and 1 severe reaction to each 4,269 injections. The incidence of each type of reaction is detailed.

*Reactions to Mapharsen.*—The most recent compilation of data for the United States Navy concerning reactions to arsenicals is presented

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94. Doak, G. O.: On the Supposed Detoxifying Effect of Various Substances Used in Association with the Arsphenamines, *Am. J. Syph., Gonorr. & Ven. Dis.* **25**:286 (May) 1941.

95. Waugh, J. R., and Milovich, E.: Severe Reactions to Arsphenamine Among 3,050 Previously Untreated Patients, *Ven. Dis. Inform.* **21**:389 (Dec.) 1940.

96. Stephenson, C. S.; Chambers, W. M., and Anderson, L. T.: Toxic Effects of Arsenical Compounds as Administered in United States Navy in 1939, *U. S. Nav. M. Bull.* **38**:587 (Oct.) 1940.

by Stephenson and his co-workers.<sup>97</sup> Between 1935 and 1939, 121,689 injections of mapharsen were administered, without fatality.

*Reactions to Tryparsamide.*—The impression has been gained from previous reports, some of them based on large series of patients, that the total subjective and objective ocular reactions from tryparsamide were in the neighborhood of 10 to 15 per cent and, further, that late reactions do occur but are relatively infrequent. The following reports, which have appeared in the literature this year, would suggest either that the figures in the past reports are too low or that the toxicity of the drug has increased considerably in the past few years. Because reports of other toxic reactions from tryparsamide have been more frequent since 1934 one must not dismiss the latter possibility too lightly.

In an attempt to clarify the discordance of opinion regarding the effect of tryparsamide on the optic nerve, Powell and Smith<sup>98</sup> selected a group of 16 patients for detailed study of the visual fields before and after the administration of the drug. Three patients did not have syphilis; the conditions of the remainder were diagnosed as syphilitic meningoencephalitis. Visual fields were mapped one to four times preceding the first injection of tryparsamide, and an average of these readings was taken as the initial position of the fields. Tryparsamide was administered intravenously in a first dose of 1.5 Gm. and in subsequent doses of 3.0 Gm. at weekly intervals. So far as possible, the mapping of the visual fields was repeated prior to each injection of tryparsamide for three to eleven serial observations. In 11 of the 16 patients studied tryparsamide therapy was associated with a constriction of the visual fields; this was marked in 2 patients and less pronounced, but consistent, in 9 others. Three patients showed no appreciable change in the fields, and the remaining 5 showed at first an apparent expansion in the visual fields, which was later followed by constriction. Presumably, none of the patients suffered antecedent disease of the optic nerve, and therefore the observations here reported are unique in the high incidence of damage to the visual apparatus as measured by constriction of the visual fields in patients under treatment with tryparsamide.

Downs, McDermott and Webster<sup>99</sup> record reactions to tryparsamide among 223 patients given 5,353 injections. Visual reactions occurred in no less than 23.3 per cent and nitritoid reactions in 13.5 per cent of all patients. An important and hitherto little recognized finding was the relative frequency of visual reactions occurring late in the course of

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97. Stephenson, C. S.; Chambers, W. M., and Anderson, L. T.: *Toxic Effects of Arsenical Compounds as Employed in Treatment of Diseases in United States Navy*, 1939, U. S. Nav. M. Bull. **39**:139 (Jan.) 1941.

98. Powell, L. S., and Smith, H. S.: *Studies of the Visual Fields in Connection with Tryparsamide Therapy*, Arch. Ophth. **24**:276 (Aug.) 1940.

99. Downs, W. G.; McDermott, W., and Webster, B.: *Reactions to Tryparsamide*, Am. J. Syph., Gonorr. & Ven. Dis. **25**:16 (Jan.) 1941.

therapy. Thirty-one per cent of these reactions occurred after 10 or more injections.

Beerman and Shaffer<sup>100</sup> record the reactions which occurred in a small group of 113 patients who received tryparsamide. Sixteen patients sustained systemic reactions, and 32 patients sustained either subjective or objective ocular reactions. The number of objective as contrasted with merely subjective ocular reactions is not stated. In 7 patients the onset was late in the course of treatment, after 15 or more injections. In no case did permanent amblyopia develop.

Turvey<sup>101</sup> has analyzed the cases of 553 patients treated with tryparsamide in the venereal disease clinics of British Columbia. He reports toxic amblyopia occurring late in 13 instances. These reactions occurred after injections numbering 20, 28, 37, 55, 16, 42, 35, 14, 45, 18, 23, 52 and 33, respectively.

*Reactions to Potassium Iodide.*—Stewart and Smith,<sup>102</sup> thoroughly familiar with the role of the potassium ion in cardiac physiology, electrocardiographically studied 5 patients who were receiving therapeutic amounts of potassium salts. The following electrocardiographic changes were noted: sinus tachycardia, supraventricular paroxysmal tachycardia, complete auriculoventricular dissociation with irregularity of the ventricles suggesting ventricular fibrillation, progressive first degree heart block and auricular standstill. Three of the 5 patients studied showed changes in the form of the T waves and RT segments which were thought to be due to coronary occlusion until their association with potassium iodide was realized. The authors assert:

Because of the widespread use of potassium iodide in the treatment of cardiovascular syphilis and of hypertension, it is not out of place to emphasize that its use is not without danger, as these changes in form of the electrocardiogram and in rhythm demonstrate. The most alarming toxic effect in its implications is the occurrence of a rhythm which has certain features similar to ventricular fibrillation. It is possible that certain accidents in patients suffering from syphilitic heart disease in the past may have occurred as a result of toxic effects of potassium on the heart.

#### CONTACT INVESTIGATION

As to contact investigation, Dyar and Guthrie<sup>103</sup> state:

Contact investigation activities have become widespread with the advent of extensive syphilis control programs in many states and municipalities. The evalua-

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100. Beerman, H., and Shaffer, B.: Reaction to Tryparsamide: Review of Ten Years' Experience, *Brit. J. Ven. Dis.* **16**:145 (July-Oct.) 1940.

101. Turvey, S. E. C.: Rare Ocular Reactions to Tryparsamide, *Am. J. Syph., Gonorr. & Ven. Dis.* **25**:623 (Sept.) 1941.

102. Stewart, H. J., and Smith, J. J.: Changes in the Electrocardiogram and in the Cardiac Rhythm During the Therapeutic Use of Potassium Salts, *Am. J. M. Sc.* **201**:177 (Feb.) 1941.

103. Dyar, R., and Guthrie, N. W.: Factors Affecting Results of Contact Investigation in Syphilis Clinic of Johns Hopkins Hospital, *Am. J. Syph., Gonorr. & Ven. Dis.* **25**:215 (March) 1941.

tion of the various methods used and the results obtained are of increasing importance. For purposes of economy and efficiency, it is desirable to limit the application of contact investigation to such groups as will yield worthwhile results. This is a question of individual judgment; the determination of the group to be followed, the methods to be used, and the amount of effort to be devoted to the average contact should be largely determined by the type of community and the available clinic and social service personnel.

The authors summarize the results of their own study as follows:

1. The investigation of the contacts of 133 cases of infectious syphilis led to the discovery of 72 previously unrecognized cases of syphilis. Forty-two of these were primary or secondary syphilis, a ratio of infectious contact cases to original cases of 32:100.

2. There were, in addition, 69 previously known cases of syphilis among the contacts named, or 52 per 100 original cases. Fifty-two of the contacts examined did not have syphilis, a ratio of 39 per 100 original cases.

3. Compared with an earlier study from this clinic, an increase in the average number of contacts named and an increase in the proportion of contacts named and an increase in the proportion of contacts examined per original case was not accompanied by an increase in the proportion of infectious contact cases or in the proportion of total new cases of syphilis discovered.

4. Of all infectious contact cases discovered, 29 per cent were under medical observation within one week following admission of the original case, and 67 per cent within one month.

5. Examination of the contacts of 53 cases of latent syphilis in colored males and females less than twenty-five years of age revealed only 1 infectious and 5 latent cases of syphilis. The ratio of infectious contacts discovered in 100 original cases is thirteen times as great for original infectious cases as for original latent cases.

Clark<sup>104</sup> records the results of contact investigation in the cases of 824 patients with acquired syphilis. The investigation of sexual contacts of 204 patients with primary or secondary syphilis led to the discovery of 213 persons with infectious or potentially infectious syphilis. Similar investigations of 100 patients with early latent syphilis yielded 59 persons with infectious or potentially infectious syphilis. The examination of 191 marital sexual contacts of 520 patients with late syphilis yielded 95 persons with syphilis in 46 of whom the disease had been previously diagnosed. In only 4 of these 95 patients was the syphilis infectious or potentially infectious. Forty-seven persons with infectious or potentially infectious syphilis were found among family contacts of the patients with early syphilis, and only 10 were found by family investigation of the group with late syphilis.

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104. Clark, E. G.: Epidemiologic Investigations in Series of Nine Hundred and Ninety-Six Cases of Acquired Syphilis, *Ven. Dis. Inform.* **21**:349 (Nov.) 1940.

## EARLY SYPHILIS

*Infectiousness.*—Pariser<sup>105</sup> reports the results of local dark field examination and mouse and rabbit inoculation of the vaginal secretions of 30 untreated syphilitic women. In 7 instances syphilis was produced in animals. Five of these patients had local cervical lesions. The sixth positive result was obtained from menstrual blood of a patient with secondary syphilis. The seventh positive result was obtained from a pregnant patient with secondary syphilis; local lesions were absent, but the cervix was edematous. In all except the last patient the dark field examination was positive for *S. pallida*. The author concludes that infectiousness through the vagina is periodically recurrent and depends on the presence or absence of local lesions.

*Primary Syphilis.*—Thurmon<sup>106</sup> reviews the clinical manifestations of primary syphilis, pointing out the variability both of the lesion and of its location, with emphasis on the impracticability either of diagnosing syphilis or of excluding it as a possibility on clinical grounds alone. Perhaps his most important statement, however, is as follows:

To diagnose a case as chancroid without completely excluding syphilis is an unsafe procedure. In approximately 54 per cent of infections of this type the two conditions are coexistent and syphilis is the major problem.

In reporting a case of primary syphilis of the vaginal wall, Tello<sup>107</sup> emphasizes the relative rarity of this condition. The patient in this case was 1 of 35 women with genital chancres; in the other 34 patients the chancre occurred on the labia, the cervix or the perineum. In the reported experience of other authors chancres of the vaginal wall are even less common than would be indicated by this small series, and although the present author does not attempt to collate the figures from the literature, these previous studies have given an incidence of such chancres of the order of magnitude of about 0.5 per cent.

*Secondary Syphilis.*—During a period in which there were 419 admissions to Bellevue Hospital for early syphilis, Thomas and Goldstein<sup>108</sup> observed 23 patients with severe chronic syphilitic tonsillitis as the only manifestation of early syphilis. The diagnosis had been missed in 20 cases in the sense that the patient had made one or more

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105. Pariser, H.: Transmissibility of Syphilis: Infectiousness of Vaginal Secretions and Menstrual Blood of Women, *J. Invest. Dermat.* **3**:375 (Oct.) 1940.

106. Thurmon, F. M.: The Clinical Manifestations of Primary Syphilis, *New England J. Med.* **223**:439 (Sept. 19) 1940.

107. Tello, E. E.: Sífilis primaria de vagina (chancro ulceroso de fondo de saco anterior), *Rev. argent. dermatosif.* **24**:567, 1940.

108. Thomas, E. W., and Goldstein, D. H.: Chronic Tonsillitis in Secondary Syphilis: Differential Diagnosis from Diphtheria and Vincent's Infection; a Report of Twenty-Three Cases, *New York State J. Med.* **41**:256 (Feb. 1) 1941.

visits to a physician or a clinic complaining of sore throat, without the possibility of syphilis being seriously considered.

There were 15 instances of membranous tonsillitis and 8 of the ulcerative or follicular type. The lesions were bilateral in all cases. Marked hoarseness was present in 2 and a history of severe dysphagia was noted in 3. The duration of symptoms prior to diagnosis was under two weeks in 5 cases and from two to three weeks in 4 cases; 12 had symptoms for a period of from 4 to 8 weeks, and 2 had symptoms for over 3 months. Three patients had been isolated because of a diagnosis of diphtheria and 1 had received diphtheria antitoxin before the discovery of syphilis.

*Blood Cells.*—There have been numerous reports in the past describing the number and type of blood cells associated with syphilitic infection. There are nearly as many different ideas regarding the blood picture found in syphilis as there are reports. Wile, Isaacs and Knerler<sup>109</sup> review some of the papers discussing the hematologic findings in early syphilis, and to clarify the subject they have studied the blood of 36 patients with early syphilis. As many as forty-five counts were made on each patient over a period of a few hours to five months after treatment was instituted. Besides studying the blood of these patients, the authors studied the blood of 2 normal and 6 syphilitic rabbits. They conclude as follows:

1. The blood cells were studied in early active syphilis in human beings (36 cases) and early active experimental syphilis in rabbits (9 [sic] cases).
2. The previously reported data including mild anemia of the secondary type, monocytosis, and eosinophilia are noted.
3. The frequent occurrence of plasma cells not recorded in earlier articles is reported.
4. A type of cell not previously recorded, but similar to that seen in infectious mononucleosis, is noted.

*Cerebrospinal Fluid.*—Merritt<sup>110</sup> points out that whereas laboratory evidence of involvement of the central nervous system can be found in approximately 40 per cent of patients with untreated early syphilis, clinical symptoms or signs of this involvement are rare. The abnormalities are of significance as they serve to establish a more serious prognosis for the individual patient.

In many of these patients the abnormalities will respond to routine treatment for early syphilis, so that in clinical practice, where perhaps only one examination of the cerebrospinal fluid can be performed on each patient, that examination should be conducted at the end of eighteen

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109. Wile, U. J.; Isaacs, R., and Knerler, C. W.: Blood Cells in Early Syphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **25**:133-141 (March) 1941.

110. Merritt, H. H.: The Early Clinical and Laboratory Manifestations of Syphilis of the Central Nervous System, *New England J. Med.* **223**:446 (Sept. 19) 1940.

months of routine treatment, the patient to be probated if all results are normal and specialized methods of treatment to be utilized if abnormalities are present.

*Treatment of Early Syphilis.*—Padget<sup>111</sup> analyzes in two important papers the long term follow-up observations on a large number of patients treated for early syphilis. In one of these<sup>111b</sup> the author summarizes his material as follows:

1. Survey of the literature revealed that there was no satisfactory long-term evaluation of the results of attempts to treat patients with early syphilis by modern methods. It seemed desirable, therefore, to analyze in detail the material which provides the basis of the present study.

The material was made up of 551 patients who came under treatment with early syphilis and who were completely re-examined 5 or more years after the termination of their original treatment. The period of post-treatment observation was more than 5 but less than 10 years (mean 7.6 years) in 278 patients, and was more than 10 years (mean 14 years) in 273 patients. The mean period of observation was 10.8 years for the group as a whole.

2. The age distribution of the patients on admission revealed nothing of significance, but the race and sex distribution showed a higher incidence of colored women, at the expense of men of both races, than was typical for the clinic from which the patients were drawn. For this and other reasons, therefore, the material of the study cannot be considered a random sample. The effort was made to nullify this objection by careful definition of all collateral and conditioning factors.

3. Comparison of the results of examination approximately 5 years and 10 or more years after the original treatment for early syphilis in the 268 patients on whom such comparative examinations were made revealed no patient with a less satisfactory result at the latter examination than at the former. This finding is thought to be of crucial importance and is therefore emphasized.

4. Analysis of the final outcome by race and sex revealed no significant differences in the incidence of "cure." Among those who did not achieve "cure," however, neurosyphilis was two and one-half times as frequent among the whites. The Negroes suffered cardiovascular syphilis more often, but the majority of the unsatisfactory results observed in this race consisted in the persistence of a positive serologic test for syphilis in the blood without other manifestations of the disease. The analysis by sex revealed one equally striking difference; among those who did not gain "cure," neurosyphilis was more than two and one-half times as common among men as among women.

5. A contrast between the final outcome for the men and for the nonparous and parous women revealed a higher percentage of favorable results in the last group than in either of the first two. The differences, however, are border line in statistical significance.

6. Elevation of the blood pressure did not prejudice the prospects of attaining "cure" for the 53 patients who sometime or always were found to have a systolic pressure above 145 mm. of mercury.

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111. Padget, P.: (a) Long Term Results in the Treatment of Early Syphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **24**:692 (Nov.) 1940; (b) Long-Term Results in the Treatment of Early Syphilis, *J. A. M. A.* **116**:7 (Jan. 4) 1941.



7. The presence of abnormalities in the cerebrospinal fluid was found greatly to reduce the percentage of "cures" attained, and in proportion to the severity of the abnormalities.

8. Among the 534 patients who received treatment of any kind, the best results were observed among those who began treatment during the seronegative primary stage, of whom 82 per cent achieved "cure." The worst results were seen among patients whose treatment was begun in the seropositive primary stage, of whom only 55 per cent were so fortunate. Among patients with secondary syphilis when treatment was begun, 68.8 per cent were "cured," and in those with early latent syphilis "cure" was gained by 58.7 per cent. These differences are probably to be explained on the basis of the immune reaction of the host to the parasite and its disruption by treatment, and emphasis is placed on the fact that, while the incidence of "cure" was higher in the patients who came under treatment with secondary syphilis than among those in the early latent group, the incidence of a persistently positive serologic test for syphilis without other evidence of the disease is more than twice as great in the latter as in the former. On the other hand, neurosyphilis was more than twice as common among those who began treatment with seropositive primary syphilis as among the others, and accounted entirely for the increased incidence of unsatisfactory results in this group.

9. Similarly, the best results were observed in the patients who came under treatment with syphilis of less than 1 month's duration, while the worst results were seen in those whose treatment began during the second month of the disease.

10. The development of early or intermediate relapse was found to be of grave prognostic significance. "Cure" was nearly three times as common among those who were not observed to relapse as in those who were, and neurosyphilis was approximately six times as common among the latter.

11. "Cure" was attained by 83.4 per cent of the patients whose treatment during the first 6 months was by a continuous system, and this increased to 90.4 per cent if treatment during the second 6 months was likewise continuous.

12. This is in sharp contrast to intermittent and irregular treatment, of which the former is approximately equal to no treatment at all (35.3 per cent spontaneous "cure") and the latter is no better. In view of this and other considerations, the question is raised as to whether, if the patient will not cooperate to receive regular treatment, it would not be better to give no treatment at all rather than irregular or intermittent treatment.

13. Detailed study of the relationship between the amount of treatment given and the time period over which it was received revealed that the final outcome depended in a directly quantitative fashion, not only on the number of doses of arsphenamine received, but also inversely upon the time span during which they were given. Thus the patients who received seven to nine injections of arsphenamine during the first 3 months did as well as those who had twice as much treatment scattered over the first 2 years.

14. There was no evidence for "esophylaxis" in this group, nor was it apparent that serious treatment reactions encouraged lapse from treatment. Those who had sustained serious treatment reactions did on the average just as well as, but no better than, those who had not.

15. The material of this study would indicate that serologic testing is not sufficient to determine the true status of patients who were treated for early

syphilis in the past; and that complete and painstaking periodic physical examination is likewise essential.

Vonderlehr <sup>112</sup> stresses the importance of continuous and prolonged treatment for early syphilis. He discusses the advantages of this treatment scheme and the disadvantages of the intermittent plan of treatment, particular stress being laid on the high incidence of relapse in cases of syphilis of the mucocutaneous surfaces and of the central nervous system when intermittent or irregular treatment is given for early syphilis.

The writer of an editorial <sup>113</sup> calls attention to the great difficulties that a peripatetic patient sometimes encounters in receiving proper antisyphilitic treatment. Because of the necessity of consultation with a number of physicians, he is frequently subjected to change in the type and manner of treatment and to differences of opinion at times legitimate and at other times born of ignorance. As a result, the patient is often hopelessly confused as to the proper course to follow and frequently abandons his antisyphilitic treatment altogether. The author states:

There is an easy and perfectly satisfactory solution for this problem. The physician who inaugurates treatment should provide the patient with a series of documents, including (1) a copy of his history and the record of his physical examination, to spare him the necessity of repeating this in detail to each new physician; (2) a written outline of treatment, planned as definitely as possible with dates, drugs, and dosage for several months in advance, and to be followed, barring unforeseen complications, by each of the physicians in each town (secured from the American Medical Directory) on the patient's itinerary, together with a blanket letter of introduction. This letter should specify the fee which the patient is able to pay for various treatment procedures.

This system retains the management and direction of the patient's treatment, and the responsibility for the ultimate outcome, in the hands of a single physician, where it properly belongs. It is assumed that the directing physician is competent to direct and carry out antisyphilitic treatment; even if he is not, it is often true that bad advice from a single source is better than conflicting good advice from many sources.

The duty of the various physicians to whom the patient may be referred is plain. They must carry out exactly the treatment procedure which the directing physician has indicated, unless of course some unforeseen complication makes this impossible. The treatment given should be recorded as to date and dosage on the record to be retained by the patient, and returned ultimately to the original physician.

*Massive Dose Method of Treatment.*—At a conference on massive dose arsenotherapy of early syphilis by the continuous intravenous drip

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112. Vonderlehr, R. A.: Continuous Alternating Scheme in Control of Acquired Syphilis, *Illinois M. J.* **79**:80 (Jan.) 1941.

113. The Treatment of the Peripatetic Patient, editorial, *Am. J. Syph., Gonorr. & Ven. Dis.* **25**:643 (Sept.) 1941.

method, Baehr <sup>114</sup> reported the results obtained with neoarsphenamine. Leifer <sup>115</sup> discussed the technic of administration, Chargin <sup>116</sup> reported the toxic manifestations in 111 patients treated with neoarsphenamine and 270 patients treated with mapharsen and Hyman <sup>117</sup> presented tentative results in patients treated with mapharsen. Of 157 patients followed six to eighteen months after the administration of 400 to 1,100 mg. of mapharsen, treatment was acknowledged a failure in 23 (15 per cent). By the most severe standards, there were 72 per cent the course of whose illness indicated a favorable trend. The second group in the mapharsen series consisted of 100 patients who had received 1,200 mg. of the drug, all of whom had been observed less than six months. Mahoney <sup>118</sup> discussed briefly the serologic observations on all these patients, and Webster <sup>119</sup> and Thomas <sup>120</sup> reported on follow-up studies. Sobotka and others <sup>121</sup> presented the results of determinations of arsenic in the blood and the urine. Rice <sup>122</sup> closed the symposium with a discussion of the possibilities of this newer method of therapy for the control of infectiousness in syphilis. Hyman <sup>123</sup> compares the results of this method

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114. Baehr, G.: Massive Arsenotherapy in Early Syphilis by Continuous Intravenous Drip Method: Preliminary Work with Neoarsphenamine, *Arch. Dermat. & Syph.* **42**:239 (Aug.) 1940.

115. Leifer, W.: Massive Arsenotherapy (Using Mapharsen) in Early Syphilis by Continuous Intravenous Drip Method: Technic, *Arch. Dermat. & Syph.* **42**:245 (Aug.) 1940.

116. Chargin, L.: Massive Arsenotherapy (Using Mapharsen) in Early Syphilis by Continuous Intravenous Drip Method: Toxicologic Manifestations, *Arch. Dermat. & Syph.* **42**:248 (Aug.) 1940.

117. Hyman, H. T.: Massive Arsenotherapy in Early Syphilis by Continuous Intravenous Drip Method: Clinical Considerations, *Arch. Dermat. & Syph.* **42**:253 (Aug.) 1940.

118. Mahoney, J. F.: Massive Arsenotherapy in Early Syphilis by Continuous Intravenous Drip Method: Résumé of Serologic Observations, *Arch. Dermat. & Syph.* **42**:262 (Aug.) 1940.

119. Webster, B.: Massive Arsenotherapy in Early Syphilis by Continuous Intravenous Drip Method: Follow-Up Observations at New York Hospital, *Arch. Dermat. & Syph.* **42**:264 (Aug.) 1940.

120. Thomas, E. W.: Massive Arsenotherapy in Early Syphilis by Continuous Intravenous Drip Method: Follow-Up Observations at Bellevue Hospital, *Arch. Dermat. & Syph.* **42**:267 (Aug.) 1940.

121. Sobotka, H.; Mann, W., and Feldbau, E.: Massive Arsenotherapy in Early Syphilis by Intravenous Drip Method: Arsenic Excretion in Urine and Concentration in Blood, *Arch. Dermat. & Syph.* **42**:270 (Aug.) 1940.

122. Rice, J. L.: Massive Arsenotherapy in Early Syphilis by Continuous Intravenous Drip Method: Public Health Aspects, *Arch. Dermat. & Syph.* **42**:283 (Aug.) 1940.

123. Hyman, H. T.: Massive Dose Chemotherapy by Intravenous Drip Method. *Bull. New York Acad. Med.* **17**:135 (Feb.) 1941.

with the results of standard treatment methods. Baehr <sup>124</sup> asserts that this method should not be adopted generally, pending wider toxicologic experience.

In commenting on the foregoing work the Council on Pharmacy and Chemistry <sup>125</sup> of the American Medical Association states:

The public health aspects of this new departure in syphilis therapy are tremendous in their possibilities of rapid sterilization of early contagious syphilis. On the other hand, results in syphilis therapy cannot be determined overnight, and a system that still gives evidence of possible hemorrhagic encephalitis in one of apparently every hundred cases treated is by no means a foolproof procedure.

In the opinion of the Council on Pharmacy and Chemistry the work of Chargin, Hyman, Rice and Leifer with continuous intravenous drip massive doses of arsenicals in the treatment of early syphilis offers great possibilities. In view of the frequency of toxic reactions, some of them grave in type, the Council believes a conservative attitude of the medical profession to be advisable. Such a form of syphilis therapy is still in the experimental stage. . . .

Schoch and Alexander <sup>126</sup> have attempted to modify the short term intensive treatment of syphilis so that patients may be treated while ambulatory with full therapeutic doses of mapharsen. Nine patients were given twenty doses of mapharsen, each 0.060 Gm., within thirty days. This treatment scheme was later modified so that each patient was given daily for ten consecutive days two 60 mg. doses of mapharsen one-half hour apart. Twenty patients were treated by this method. None of the 29 patients experienced a severe treatment reaction. At the time treatment was instituted, 3 patients were in the seronegative primary stage, 10 were in the seropositive primary stage and 16 had secondary syphilis. At the end of ten weeks 14 of the 29 patients were seronegative. The serum of the remaining 15 showed a steady decline in reagin content, and at the end of seven months 12 of these 15 patients were seronegative. One of the 26 seronegative patients had a reinfection and another a relapse; both patients were retreated. Two patients experienced a serologic relapse, both of whom had abnormal spinal fluid (the only spinal fluid observed which gave a positive reaction for syphilis).

Raulston and Magnuson, <sup>127</sup> in a preliminary report on the concentration of arsenic in the tissues of experimental animals, emphasize the

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124. Baehr, G.: Possibilities for Control of Syphilis with Intravenous Drip Technic of Massive Arsenotherapy, *Am. J. Pub. Health* **31**:176 (Feb.) 1941.

125. Chemotherapy by Massive Dose Intravenous Drip, preliminary report of Council on Pharmacy and Chemistry, *J. A. M. A.* **115**:857 (Sept. 7) 1940.

126. Schoch, A., and Alexander, L. J.: Short Term Intensive Arsenotherapy of Early Syphilis: Preliminary Report, *Am. J. Syph., Gonor. & Ven. Dis.* **25**:607 (Sept.) 1941.

127. Raulston, B. O., and Magnuson, H. J.: Concentration of Arsenic in the Tissues of Experimental Animals Following Intravenous Injection of Massive Doses of Arsenic by Continuous Drip Method, *Tr. A. Am. Physicians* **44**:255, 1940.

need for such experimental work following the administration of large amounts of arsenic during a relatively short period. They record<sup>128</sup> the results of giving dogs doses of arsenic comparable to the dose used in man by the intravenous drip method. They state:

The amounts of arsenic found in the blood indicate that following repeated doses of mapharsen the arsenic does not leave the blood as rapidly as it does following single doses of neoarsphenamine and that by frequently repeated doses a high concentration of arsenic may be maintained. . . . The accumulation, as observed in our experiments apparently is not due to kidney damage, as indicated by the continued excretion of large amounts of arsenic in the urine and the absence of histological evidence of important changes in these organs. It may be assumed that the tissues reach a saturation point after which they absorb less arsenic from the blood stream.

The maximum concentrations of arsenic in the blood during and immediately following these injections were not determined, as we were interested primarily in the minimum levels maintained. That the maxima became progressively higher is suggested by the values obtained one half hour after the tenth dose of each day. By the end of the fourth day this level had reached 150 micrograms per cent of arsenic in contrast to a level of 73 micrograms per cent at the end of the first day. . . .

In view of the enormous concentrations of arsenic in the gall-bladder bile we believe that the greater part if not all of the arsenic contained in the feces reaches the bowel through the bile. . . . That the removal of arsenic by the liver and excretion in the bile must be quite efficient is indicated by the fact that the concentration of arsenic in the liver does not rise above the level reached during the first day of injection in spite of continued injection of large amounts during the next three days.

The concentrations of arsenic obtained in the tissues are most interesting. With but four exceptions, there is a tendency for the arsenic concentration in the tissues to parallel that of the blood. These four exceptions are brain, liver, kidney, and bone. . . .

The concentrations of arsenic in the liver and in the kidney are not surprising in view of the known excretory functions of these organs. That the concentration in the liver reaches a maximum during the first day must indicate that the capacity of the liver to excrete the arsenic through the bile is equal to, or greater than, its capacity to selectively remove the arsenic from the blood stream.

Arsenic in the gall-bladder disappeared very rapidly following the cessation of mapharsen. The arsenic content of the liver dropped much more rapidly than that of the kidney. This apparently indicates that after the initial large amounts of arsenic have been excreted, the major portion of the remaining arsenic is excreted through the kidney rather than the liver.

The deposition of arsenic in the bones is a phenomenon which has been emphasized but little, especially in the American literature. . . .

These findings are in accord with our observations that there is an accumulation of arsenic in bones which reaches its maximum after arsenic administration has

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128. Magnuson, H. J., and Raulston, B. O.: The Concentration of Arsenic in Tissues and the Excretion of Arsenic by Experimental Animals Following Intravenous Injection of Massive Doses of Mapharsen, *Ann. Int. Med.* **14**:2199 (June) 1941.

been stopped and while the arsenic concentration in other tissues is falling. This would indicate a second mobilization of the arsenic with secondary deposition in the bone. . . .

One is of course tempted to estimate whether the concentrations of arsenic obtained in the tissues are spirocheticidal. . . . Taking 1:1,000,000 as the spirocheticidal level would mean a level of 29 micrograms of arsenic per 100 grams of fresh tissue calculating mapharsen on the basis of 29 per cent arsenic content and further assuming that all of the arsenic in the tissues is in the form of mapharsen. This would mean that all of the tissues examined with the exception of the central nervous system had during the four day treatment period concentrations of arsenic which were spirocheticidal. . . .

Of definite significance is the absence of serious damage to the tissues by the large doses of mapharsen as seen in the microscopic sections. While these findings are very encouraging, it is emphasized once again that this is but a single step of the many suggested at the beginning of this paper which should be taken before more general use is made of this method in the treatment of human syphilis.

By a set of appropriate and carefully conducted experiments, Magnuson and Raulston<sup>129</sup> determined that the maximum tolerated dose of mapharsen when given to dogs by the continuous drip method for five consecutive days is 10 mg. per kilogram of body weight per day. Similarly, the minimum lethal dose under the same conditions is 12 mg. per kilogram per day. Since the dose of mapharsen which has been used in the continuous drip treatment of syphilis in human beings approximates 4 mg. per kilogram of body weight per day for a five day period, this produces a situation in which the safety factor (maximum tolerated dose/usually administered dose) is only 2.5, as opposed to the safety factor of 12 for mapharsen given by the usual single injection dose. They conclude, therefore, that there is need for considerable caution in the administration of massive doses of mapharsen to patients by the continuous drip method.

#### TRANSFUSION SYPHILIS

Bulfamonte<sup>130</sup> reports another case of transfusion syphilis. The sequence is much like that in many of the other reported cases. A 25 year old white woman was the recipient of 500 cc. of her brother's blood. At the time the transfusion was given the brother had a negative serologic reaction for syphilis. Careful investigation of the brother after syphilis had developed in the recipient revealed that he had seronegative primary syphilis.

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129. Magnuson, H. J., and Raulston, B. O., with the technical assistance of Muff, A.: The Toxic Dose of Mapharsen Given by the Continuous Drip Method, *Ven. Dis. Inform.* **22**:157 (May) 1941.

130. Bulfamonte, J. C.: Blood Transfusion Syphilis: Report of a Case, *Arch. Dermat. & Syph.* **44**:23 (July) 1941.

That this too frequent tragedy is now preventable since the advent of the blood bank and the general use of dried plasma is illustrated by the following reports.

In a footnote to a general discussion of the problems of the preservation, storage and subsequent administration of human blood, the so-called "blood bank" procedure, Kolmer<sup>131</sup> states:

An additional advantage in the use of preserved blood may be greater safety from the danger of transfusion syphilis. I have inoculated 10 cc. of fresh citrated blood with 1 cc. of a heavy suspension of virulent *Treponema pallidum* (Nichols-Hough strain) from acute testicular syphilomas of rabbits showing approximately 200 treponemes per dark field. A rabbit inoculated at once with 1 cc. of the citrated-blood-treponeme mixture intratesticularly, as well as rabbits inoculated one and three hours later, developed acute testicular syphilis in about five to six weeks. Rabbits inoculated one, two seven, fourteen, and twenty-eight days later (the mixture being kept at 4° to 6° C.) escaped testicular infection, and lymph gland transfers to fresh rabbits made six weeks later were negative. The results indicate, therefore, that *Treponema pallidum* in citrated blood may die after twenty-four hours of preservation at 4° to 6° C.

Turner and Discker<sup>132</sup> also feel that it is probable that the use of stored blood for transfusions further reduces the risk of transfusion syphilis and report a series of investigations calculated to determine that point. Human blood inoculated with *S. pallida* failed to give rise to infection in normal rabbits after storage periods of forty-eight hours or longer. Virulent treponemes added to citrated whole rabbit blood were infectious for normal rabbits after forty-eight hours' storage but not after seventy-two hours or longer.

Bloch<sup>133</sup> reports a series of experiments which demonstrate that in fairly heavy suspension in citrated blood stored at a temperature of 5 C. *S. pallida* may survive for as long as seventy-two hours. Blood-spirochete mixtures stored for ninety-six hours or longer, however, were not infectious for other rabbits.

In order to determine whether *S. pallida* or *Spirochaeta pertenuis* remained viable in desiccated serum, Turner, Bauer and Kluth<sup>134</sup> carried out well controlled experiments, which they summarize as follows:

In recent experiments, the infectivity of virulent *T. pallidum* suspended in rabbit serum was tested before and 3 to 5 days after desiccation. Material from each of

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131. Kolmer, J. A.: Preserved Blood "Banks" in Relation to Transfusion in the Treatment of Disease, *J. Lab. & Clin. Med.* **26**:82 (Oct.) 1940.

132. Turner, T. B., and Discker, T. H.: Duration of Infectivity of *Treponema pallidum* in Citrated Blood Stored Under Conditions Obtaining in Blood Banks, *Bull. Johns Hopkins Hosp.* **68**:269 (March) 1941.

133. Bloch, O., Jr.: Loss of Virulence of *Treponema Pallidum* in Citrated Blood at 5° C., *Bull. Johns Hopkins Hosp.* **68**:412 (May) 1941.

134. Turner, T. B.; Bauer, J. H., and Kluth, F. C.: The Viability of the Spirochetes of Syphilis and Yaws in Desiccated Blood Serum, *Am. J. M. Sc.* **202**:416 (Sept.) 1941.

9 specimens produced lesions in rabbits before desiccation. Three to 5 days after freezing and drying in an efficient desiccating apparatus, rabbits were inoculated with from 6 to 65 times the amount used for the control animals. None of 18 rabbits inoculated with desiccated material developed a syphilitic lesion, and their lymph nodes were not infectious for normal rabbits. Of 6 rabbits similarly inoculated with desiccated *T. pertenue* from 3 different sources, none developed lesions, and their lymph nodes were not infectious for normal rabbits.

Eichenlaub and his collaborators<sup>135</sup> have experimentally demonstrated that 10 mg. of mapharsen added to 500 cc. of citrated blood is sufficient to kill any spirochetes that may be present and thereby to prevent transfusion syphilis.

#### LATE SYPHILIS

*Incidence.*—Because Bruusgaard's<sup>136</sup> paper analyzing the fate of persons with syphilis who received no specific treatment has been widely quoted, Sowder<sup>137</sup> has reexamined it statistically in an effort to determine what, if any, limitations need be put on it. He asserts:

It has been demonstrated that Bruusgaard, in following up 473 of Boeck's original, 2,181 untreated syphilitic persons, to a very considerable extent selected (unavoidably for the most part) those persons most likely to show serious complications of syphilis and found too few of those that were symptom free. Bruusgaard himself evidently realized this and in several instances mentioned it in his paper. By considering these factors it is evident that the occurrence of serious complications of syphilis in Boeck's original material was low, though only approximate figures may be derived.

*Bones and Joints.*—At the Boston meeting of the American Academy of Orthopaedic Surgeons in January 1940 Weinberg<sup>138</sup> presented the analysis of several hundred cases of syphilis of bones and joints. The analyses show that the disease was most frequent in persons between the ages of 20 and 40 years and that the tibia was the most frequent site of involvement. The disease may simulate many other conditions; the onset may be gradual or sudden, and multiple lesions may often be symptomless and may be demonstrated only by roentgenologic examinations. Diagnosis in difficult cases may depend on therapeutic tests. He believes that the union of fractures is uninfluenced by syphilis.

*Esophagus.*—Kampmeier and Jones<sup>139</sup> state that while syphilitic lesions may occur in the esophagus, they are recognized infrequently.

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135. Eichenlaub, F. J.; Stolar, R., and Wode, A.: Prevention of Transfusion Syphilis, *Arch. Dermat. & Syph.* **44**:441 (Sept.) 1941.

136. Bruusgaard, E.: Ueber des Schicksal der nicht spezifisch behandelten Luetiker, *Arch. f. Dermat. u. Syph.* **157**:309, 1939.

137. Sowder, W. T.: Interpretation of Bruusgaard's Paper on Fate of Untreated Syphilitics, *Am. J. Syph., Gonorr. & Ven. Dis.* **24**:684 (Nov.) 1940.

138. Weinberg, E. D.: Syphilitic Lesions of Bones and Joints, *Surgery* **7**:968 (June) 1940.

139. Kampmeier, R. H., and Jones, E.: Esophageal Obstruction Due to Gummata of Esophagus and Diaphragm, *Am. J. M. Sc.* **201**:539 (April) 1941.



In an extensive survey of the literature in 1931, Guyot<sup>140</sup> was able to find only 55 previously reported cases of such lesions, to which he added 2 cases of his own; since that time 2 additional cases have been reported. Kampmeier and Jones feel, therefore, that their 1 case of gumma of the esophagus and 3 cases of gumma of the diaphragm with esophageal obstruction merit comment, especially since the latter syndrome has not been previously recorded. Their patients all presented themselves with symptoms of esophageal obstruction, and after an analysis of this experience and the reports in the literature, the authors conclude:

The differentiation of gummatous lesions of the esophagus or diaphragm from obstruction to carcinoma or cardiospasm can only be made by direct examination (esophagoscopy and biopsy), and the ultimate response to treatment. Antisyphilitic treatment for gummatous lesions producing esophageal obstruction may not only fail to relieve but may actually increase the obstruction ("therapeutic paradox"). Because of resultant fibrosis and contraction of scar tissue esophageal dilatation will probably be necessary.

Case 2 illustrates the importance of accurate diagnosis in esophageal obstruction. The age of the patient (69) and the results of roentgenologic examination led to the diagnosis of carcinoma, and the use of palliative treatment in spite of the fact that he was known to have syphilis. Appropriate treatment at the time the patient was first seen probably would have relieved the obstruction.

In the other 3 cases the nature of the lesion was recognized, and antisyphilitic treatment and active dilatation of the obstruction offered relief.

Finally it should be emphasized that esophageal obstruction in a case of chronic syphilis may be carcinomatous. Gummatous lesions of the esophagus or diaphragm are rare. Indeed, in individuals with syphilis, the incidence of carcinoma of the esophagus may be greater than obstructive gummatous lesions. . . . Nevertheless, the importance of accurate diagnosis and appropriate treatment is apparent. . . .

#### CARDIOVASCULAR SYPHILIS

*Incidence.*—From a review of the records of the Cincinnati General Hospital from 1926 through 1937, Gelperin<sup>141</sup> found that of the 7,683 autopsies which had been performed during this period, 700 (9.1 per cent) revealed microscopic evidence of syphilitic aortitis. The figure was fairly constant from year to year, varying from a low of 7.3 per cent in 1926 and 1934 to a high of 13.2 per cent in 1931.

As Weinstein<sup>142</sup> points out, mortality statistics which have been classified according to the International List of Causes of Death do not

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140. Guyot, R.: La syphilis de l'oesophage en particulier au point de vue anatomo-pathologique, *Ann. d'oto-laryng.*, May 1931, p. 505.

141. Gelperin, A.: The Incidence of Syphilitic Aortitis in a Representative Municipal Hospital, *Am. Heart J.* **20**:340 (Sept.) 1940.

142. Weinstein, J.: Public Health Aspects of Cardiovascular Syphilis in New York City, *New York State J. Med.* **41**:234 (Feb. 1) 1941.

make it possible to distinguish between the different etiologic types of heart disease. Lacking such information, however, he feels that one may utilize the recorded deaths from aneurysm to determine mortality trends in cardiovascular syphilis. In doing this for New York city for the years 1924 to 1938 inclusive, he found that no conspicuous change had taken place and that the incidence of death from aneurysm regularly was of the order of 2 per hundred thousand total population. Combining this with available information regarding morbidity makes it clear that cardiovascular syphilis is still an important public health problem.

*Aortic Insufficiency.*—Nichols<sup>143</sup> presents a detailed study of 70 cases of syphilitic aortic insufficiency which had been observed clinically and further analysis of 41 cases of syphilitic aortic regurgitation in which autopsy was performed.

Of the 70 cases in the series the ratio of males to females was six to one. Fifty-three of the patients were colored; 17 were white. The average age was 46.04, with extremes between 28 and 64. The average interval between primary infection and the onset of symptoms was 22 years. The most common presenting symptom was dyspnea on exertion, which occurred in 71 per cent. The rarity of paroxysmal dyspnea and pain was noted. An increase in the size of the heart was noted in 93 per cent. The average duration of symptoms before medical attention was sought was 10 months, the shortest two weeks, and the longest five years. Edema of the ankles was present in 40 per cent upon first admission to the hospital. The typical to-and-fro murmur of aortic insufficiency was present in 87 per cent. The presence of a loud musical diastolic murmur and thrill in 5 patients was discussed and its pathology explained. The average pulse pressure was 84 mm. of mercury. The Wassermann reaction was positive in 85 per cent of the patients.

*Syphilitic Aortitis and Coronary Occlusion.*—Porter and Vaughan<sup>144</sup> bring out that while occlusion of coronary arteries by thrombosis is a relatively common occurrence, occlusion by embolism is rare. Search of the literature revealed 27 previously reported cases, and their own survey of more than 3,000 autopsies disclosed 3 other instances of the condition. Their experience is extraordinary in that occlusion in each case was the indirect result of syphilitic aortitis.

In the course of a symposium on sudden death, Leary<sup>145</sup> described the characteristic manner in which syphilis invades the root of the aorta with overstimulation of growth of the vasa vasorum, which, as they penetrate through the media into the intima, are followed by an excessive growth of fibroblastic tissue. This process may be widespread in the first

143. Nichols, C. F.: A Study of Syphilis of the Aorta and Aortic Valve Area, *Ann. Int. Med.* **14**:960 (Dec.) 1940.

144. Porter, W. B., and Vaughan, E. W.: Coronary Embolism: A Complication of Syphilitic Aortitis, with Report of Three Cases, *Am. J. M. Sc.* **200**:184 (Aug.) 1940.

145. Leary, T.: Syphilitic Aortitis as a Cause of Sudden Death, *New England J. Med.* **223**:789 (Nov. 14) 1940.

portion of the aorta or may be limited; under the latter circumstance the mouth of one or both of the coronary arteries is a frequent site of predilection. At postmortem examination it may be found to be almost occluded by a syphilitic process primarily in the aorta itself, the artery just distal to the ostium being comparatively normal. Apparently in many, if not most, of the patients with such an occlusion it has occurred so slowly that collateral circulation has had time to develop, but the author points out the best collateral circulation is always a substitute circulation, liable to become insufficient under the circumstances of additional strain and to lead to sudden death of the coronary type. Rupture of an aortic aneurysm which has previously been asymptomatic occasionally produces sudden death, but this is unusual. Patients with aortic insufficiency may die suddenly from coronary insufficiency, but more commonly they suffer the consequences of unrelieved congestive heart failure.

*Dissecting Aneurysm Simulating Aortic Insufficiency.*—Gouley and Anderson<sup>146</sup> report that in the last ten years 31 cases of dissecting aneurysm of the aorta have been encountered at necropsy at the Philadelphia General Hospital (an incidence of 1 to 480 in necropsies of patients over the age of 20 years) and of these the clinical course in 6 cases differed so greatly from that commonly observed as to form the basis of the present report. In all 6 cases the patients were Negroes; 4 of the patients were men, and the ages ranged from 32 to 69 years.

All the patients had cardiac decompensation. Examination revealed hypertension, cardiac enlargement and various cardiac murmurs, but constant to all of this group was the murmur of aortic regurgitation; a Corrigan pulse and wide pulse pressure were present in every case.

The area of supracardiac dulness was widened; there was roentgenologic evidence of dilatation of the aortic arch, and despite the fact that serologic tests for syphilis gave positive reactions in only 1 of the group, a clinical diagnosis of syphilitic aortitis with aortic regurgitation was made in every case.

Necropsy in these cases surprisingly revealed the presence of dissecting aneurysm of the aorta of the chronic type. The dissected areas were completely endothelialized. There were 4 instances of "double barrel" aorta, the new channel communicating with the original at both the most proximal and the most distal portions of the vessel. In the two remaining cases, dissection remained entirely intramural, confined within the media, but extending for a considerable distance, beginning at the root of the aorta and extending into the thoracic portion of the vessel. In all six cases the new channel began either at the aortic valvular orifice or from the root of the aorta immediately above the valvular ring.

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146. Gouley, B. A., and Anderson, E.: Chronic Dissecting Aneurysm of the Aorta, Simulating Syphilitic Cardiovascular Disease: Notes on the Associated Aortic Murmurs, *Ann. Int. Med.* **14**:978 (Dec.) 1940.

The hearts were hypertrophied, their weight ranging from 420 to 900 grams. There were no abnormalities of the aortic commissures, but the aortic rings were dilated, markedly so in 3 instances. We noted also in each case a lipping or thickening of the central portions of the free margins of the aortic leaflets. The lateral portions of the leaflets adjacent to the commissures retained a normal delicacy. The central thickenings were evidently thickened *corpora aurantii*, the result, we think, of a constant "central" leakage through an aortic valve, the leaflets of which were no longer efficiently approximated in diastole.

On gross examination syphilitic aortitis was thought to be present in 3 cases; histologic examination of the aorta in the 4 cases in which adequate sections had been preserved did not reveal any evidence of syphilis but did show the typical picture of Erdheim's "medionecrosis aortae cystica." Included in this group was the 1 patient whose blood gave a positive serologic reaction for syphilis.

The authors, therefore, conclude:

Occasional cases of dissecting aortic aneurysm of the chronic type closely simulate luetic cardiovascular disease. Such patients present the signs of aortic valvular regurgitation and of aortitis. Progressive cardiac decompensation may continue for many months or even years. There is often no pain and no history of a painful attack, so that if it had been present, it was relatively slight and soon forgotten. Life is terminated by heart failure, or occasionally by a long delayed secondary aortic rupture.

The aortic valvular leakage is directly dependent on the proximity of the dissection of the valvular ring. The dilatation of the latter and of the ascending arch of the aorta, in the chronic cases suggests a loss of tonus possibly secondary to the destruction of some controlling mechanism. A "mechanical" noninfectious deformity of the aortic leaflets may result from long continued inefficient closure of the aortic valve.

Notable clinical features were (1) the persistently negative serologic tests for syphilis in the large majority, (2) the usually marked and often enormous enlargement of the heart, especially of the left ventricle and the constant dilatation of the ascending arch of the aorta, (3) the relatively high incidence of hemoptysis in chronic dissecting aneurysm showing signs of aortic regurgitation.

*Electrocardiographic Studies.*—Tung and Mu<sup>147</sup> present a study based on 22 patients with unequivocal syphilitic aortitis with aortic regurgitation, with or without aneurysm or demonstrable evidence of narrowing of the ostiums of the coronary arteries. The patients were unselected, save for the exclusion of those with marked congestive failure who did not respond to medical treatment. In addition to the usual studies appropriate to a patient with syphilitic aortic regurgitation, from one to several serial electrocardiograms were made for each of these patients, and a control electrocardiogram was made for each subject

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147. Tung, C. L., and Mu, J. W.: The Immediate Effects of the Intravenous Administration of Neoarsphenamine on the Electrocardiogram in Cases of Syphilitic Aortitis, *Am. Heart J.* **19**:529 (May) 1940.

about a half an hour before the intravenous injection of neoarsphenamine. This was repeated about four hours after treatment, and an electrocardiogram was also made just before and four hours after each subsequent weekly injection. There were in all 61 series of examinations on the 22 patients.

The authors did not observe any abnormalities developing after treatment in 15 patients, but in eleven of sixteen examinations performed on the other 5 patients mild or moderate changes in the RT or ST segments or in the T deflections occurred. The changes were not marked, though the authors feel that they were probably significant in view of the fact that they occurred so soon after the control records were made. In addition, remarkable changes occurred in the electrocardiograms of 2 patients. The records taken four hours after intravenous therapy showed a marked change in the ventricular complex of the electrocardiogram, involving in both cases a depression of the ST segments and inversion of previously upright T deflections. The changes in these 2 cases were almost identical and were not unlike those observed after coronary thrombosis or during an attack of angina pectoris. It is of considerable interest that the changes were observed to develop only once in each patient and that they followed the first injection of neoarsphenamine in 1 but came after the second injection of the fourth course of treatment in the other.

In discussing the possible mechanism by which these changes might have occurred, the authors point out that, first, there might have been a localized reaction in syphilitic inflammatory tissue around the ostiums of the coronary arteries and, second, that there might have been a direct effect of the neoarsphenamine on a presumably syphilitic myocardium. Since provable myocardial syphilis is rare and since the changes they observed simulated those seen in other cases of disease of the coronary arteries, they conclude that the changes were caused by reactions in the syphilitic aortic lesion, with resulting encroachment on the coronary artery. An ultimate evaluation of so small a group is of course not possible, but the authors believe that neoarsphenamine, when administered in small doses, exerts an immediate effect on syphilitic lesions in the aorta and that in cases of marked involvement of the coronary arteries it may exert temporarily a deleterious effect on the coronary circulation.

Berk<sup>148</sup> outlines the difficulties in diagnosing cardiovascular syphilis, particularly in the stage of uncomplicated aortitis, and points out the importance of involvement of the ostiums of the coronary arteries in the prognosis of the condition. His study is based on a group of 172 patients with conditions which had been diagnosed as some form of cardiovascular

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148. Berk, L. H.: Cardiovascular Syphilis: A Clinical and Electrocardiographic Study, *New York State J. Med.* **41**:223 (Feb. 1) 1941.

syphilis, 35 of whom were examined post mortem. One hundred and seventeen had died on whom autopsy was not performed, and 20 were still being followed. Of the 35 patients on whom autopsy was done, one or both of the ostiums of the coronary arteries were narrowed or closed in 26 (74 per cent), and in 12 patients this condition was bilateral. Regarding electrocardiographic studies, the author says:

In the electrocardiogram we have a valuable means of arriving at an early objective diagnosis in these cases. Taken in the normal manner, the electrocardiogram is normal in 95 per cent of our early [aortitis] cases. However, an electrocardiographic study made with the graduated exercise test, consisting of rapidly climbing steps, trotting, and other means of physical exertion which impose a burden on the heart, has possibilities as yet unrealized. . . .

An abnormal electrocardiogram with progressive serial changes is found to be (in the absence of acute myocardial infarction) strongly suggestive of syphilitic aortitis with probable coronary ostial stenosis.

They feel, therefore, that electrocardiographic study made with the exercise test is the only safe means of establishing the diagnosis of latent stenosis of the ostiums of the coronary arteries and recommend its routine use both in early stages of the condition and during subsequent years by systematic follow-up examinations.

*Roentgenograms.*—Scott and his collaborators<sup>149</sup> present a general discussion of the various special roentgenologic methods useful in the diagnosis and localization of aortic aneurysm and mediastinal tumor, with particular reference to body section roentgenography with an apparatus called the laminagraph. Body section roentgenography is possible by several ingenious technical methods and has the advantage of portraying the level of the mass or other abnormality under study in relief, without overlying and obliterating shadows. The authors present brief reports of 4 cases illustrative of the value of the method.

Edeiken<sup>150</sup> studied in some detail the measurements of an orthodiagram and a subsequent teleroentgenogram made at a target distance of 78 inches (198.12 cm.) for 133 patients suffering from a variety of condition. He points out that a comparison of orthodiagrams and teleroentgenograms is difficult because, first, it is impossible to be sure that the chest is in exactly the same position at the two examinations; second, the phase of respiration must unquestionably induce variation, and, third, the same is true regarding the phase of the cardiac cycle. The measurements differed rather consistently, however; in 30 of the 33 cases the transverse diameter of the heart averaged 6.6 per cent larger

149. Scott, W. G.; Moore, S., and Russell, T. G.: Body Section Radiography in the Diagnosis of Aortic Aneurysms and Mediastinal Tumors, South. M. J. 34:343 (April) 1941.

150. Edeiken, J.: A Comparison of the Orthodiagram with the Teleroentgenogram, Am. Heart J. 20:77 (July) 1940.

in the teleroentgenogram, with a range from 0 to 16 per cent. More striking were the discrepancies found in the measurements of the aorta according to the Vaquez-Bordet diameter. In 119 of 124 cases this was larger in the teleroentgenogram, varying from 2 to 27 per cent, with almost two thirds of this group falling into the range from 6 to 15 per cent.

By appropriate observations on a heart model with variation of target object and of extreme distance, the author readily substantiated the theoretic conclusion that variations in both can cause great distortion in the extreme under the conditions of teleroentgenography. At a 78 inch tube-film distance the majority of the distortion is caused by variations in the object-film distance which are conditioned by the conformation of the chest. He states:

The distortion of the heart is not great and is of little practical significance. The aorta, however, may be considerably magnified and distorted, especially in deep chests in which the object film distance of the descending aorta is increased.

#### NEUROSYPHILIS

*Association of Neurosyphilis and Late Syphilis of Skin, Mucous Membranes and Bones.*—Shaw<sup>151</sup> points out that it is a commonly accepted belief that late syphilis of the skin, mucous membranes or bones is seldom associated with syphilis of the central nervous system. He has studied 165 patients with late syphilis of the skin, mucous membranes and bones, who were seen between 1932 and 1936. The ages of these patients ranged from 20 to 69 years. Seventy (42.4 per cent) of the 165 patients had examinations of the cerebrospinal fluid before or shortly after treatment was instituted. These 70 patients are compared with a control group of 700 patients who were seen at approximately the same time. Fifteen (21.4 per cent) of the 70 patients with late cutaneous or osseous syphilis were found to have syphilis of the central nervous system. Seven of these had symptomatic and 8 asymptomatic neurosyphilis. Of the control group, 40 per cent were found to have syphilis of the central nervous system. Shaw concludes, therefore, that the incidence of neurosyphilis in patients with mucocutaneous or osseous syphilis is considerably higher than is commonly reported in the literature and emphasizes the fact that the cerebrospinal fluid should be examined in all patients with benign lesions of late syphilis.

*Relation of Diet to the Occurrence of Ataxia and Degeneration in the Nervous System of Pigs.*—In light of the present lack of information concerning the fundamental process responsible in the pathogenesis

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151. Shaw, C.: Neurosyphilis and Late Syphilis of Skin, Mucous Membranes and Bones, Arch. Dermat. & Syph. 42:456 (Sept.) 1940.

of tabes dorsalis, the observations of Wintrobe and his collaborators<sup>152</sup> are of great interest and when extended may prove to be of crucial importance. These authors raised 44 pure-bred or cross-bred pigs beginning at an average age of 3 weeks on a basal diet containing casein, sugar, lard, a mineral mixture, cod liver oil, ascorbic acid and varying amounts of yeast. The basic diet was mixed and fed in standard units per kilogram of body weight. The authors summarize their results as follows:

When the yeast content of this diet was reduced to a low level or omitted entirely, and thiamin, riboflavin or nicotinic acid were furnished separately or in various combinations, a condition developed which was characterized by disturbed gait and extensive lesions in the nervous system. These lesions were observed in each of the 18 animals fed this deficient diet.

The lesions consisted of degenerative changes in the peripheral nerves, the spinal ganglia, the posterior roots, and the dorsal funiculi of the spinal cord. They differed in degree but seemed to progress centrally, from the periphery. When these lesions were very extensive, changes were seen in some instances in the anterior horn cells as well.

Inanition alone, in the sense that relatively low amounts of carbohydrate, protein and fat were furnished, did not seem to be a cause of the degenerative changes.

Less extensive changes were observed in 2 out of 3 pigs receiving the deficient diet but supplied with a filtrate factor made from yeast. Even when whole dried yeast was furnished in large amounts, however, only 5 out of 12 pigs remained entirely free of lesions.

None of 6 pigs fed whole dessicated liver developed changes referable to the nervous system.

Wheat germ oil alone failed to protect 3 pigs given the deficient diet, but all of 5 pigs given yeast or liver in addition to wheat germ oil remained normal. It is pointed out that this does not necessarily indicate that two factors are needed to protect the nervous system of the pig.

*Pupillary Abnormalities.*—Ford and his collaborators<sup>153</sup> report a series of 5 cases which serve to illustrate the pupillary abnormalities and the paradoxical movements of the bulb and lid which may be observed as the end result of paralysis of the third nerve with regeneration. The phenomena which require explanation are (1) loss of elevation and depression of the bulb; (2) anomalous adduction of the bulb when elevation or depression is attempted; (3) preservation of adduction and abduction; (4) lifting of the lid during adduction, convergence and attempted elevation and depression; (5) drooping of the lid during

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152. Wintrobe, M. M.; Miller, J. L., Jr., and Lisco, H.: The Relation of Diet to the Occurrence of Ataxia and Degeneration in the Nervous System of Pigs, *Bull. Johns Hopkins Hosp.* **67**:377 (Dec.) 1940.

153. Ford, F. R.; Walsh, F. B., and King, A.: Clinical Observations on the Pupillary Phenomena Resulting from Regeneration of the Third Nerve with Especial Reference to the Argyll Robertson Pupil, *Bull. Johns Hopkins Hosp.* **68**:309 (April) 1941.



abduction, and (6) the pupillary reactions. The pupillary reactions fall into three different categories: 1. The pupil remains large and fixed, reacting neither to light stimulation nor during convergence. 2. The pupil contracts not only during convergence but when other movements are attempted which require the action of muscles innervated by the third nerve; there is no light reflex, and when the eye is abducted the pupil dilates. 3. The pupil behaves as in 2 but also reacts to light; in the experience of these authors, the light reflex is always slow and of small amplitude.

The authors feel that these phenomena are most easily explained on the basis of misdirection of regenerating nerve fibers which become widely distributed among muscles other than those they originally innervated.

With the report of 6 additional cases, Scheie<sup>154</sup> calls attention to the salient features of Adie's syndrome with particularly reference to the differential diagnosis between this and the Argyll Robertson phenomenon and from observations relevant to the probable location of the disturbance in the production of the tonic pupils. Of extreme interest in all of his patients with Adie's syndrome was the marked constriction of the affected pupil after instillation of a 2.5 per cent solution of mecholyl chloride (acetylbetamethylcholine hydrochloride). The same drug did not cause a reaction in the unaffected pupil or in 50 normal controls. The cases here reported otherwise were typical, so that the author postulates the site of a lesion as being an area of partial parasympathetic paralysis peripheral to the ganglion. He again emphasizes the importance of distinguishing the Adie syndrome from tabes dorsalis with Argyll Robertson pupils and suggests this reaction to acetylbetamethylcholine hydrochloride as potentially of great help in facilitating the distinction.

*Optic Atrophy.*—Hausman<sup>155</sup> discusses further the occurrence of arachnoid adhesions around the chiasm in patients with optic nerve atrophy apparently due to syphilis and points out the indications for surgical intervention under such circumstances and the benefits in the restoration or improvement of vision. He has recently observed 15 patients with "syphilitic disorders of the optic nerve," all of whom had a history or serologic evidence of syphilis, together with rapid loss of vision, frequently terminating in blindness. One patient had papilledema; 1 had secondary atrophy, and the remaining 13 patients had primary atrophy of the optic nerve. Five were operated on, and of these, 4 had the chiasm explored. Three of the latter patients mani-

154. Scheie, H. G.: Site of Disturbance in Adie's Syndrome, *Arch. Ophth.* **24**:225 (Aug.) 1940.

155. Hausman, L.: Surgical Treatment of Syphilitic Optic Atrophy Due to Chiasmal Arachnoiditis, *Am. J. Ophth.* **24**:119 (Feb.) 1941.

fested bilateral primary atrophy of the optic nerve, heteronymous visual defects or almost total blindness and a normal ventricular system, without evidence of internal hydrocephalus. All of these showed adhesions around the optic chiasm and nerve at operation. After the removal of adhesions, the vision improved in all and became normal in 1. One patient had suffered a progressive loss of vision for three years, apparently consequent to bilateral papilledema. The visual fields showed irregular concentric constriction, and there was bilateral secondary atrophy of the optic nerve. An encephalogram revealed internal hydrocephalus. Operation was performed at the patient's request; no adhesions were revealed around the chiasm. One patient presented concentric constriction of the visual fields, enlargement of the blind spots and bilateral papilledema, with normal spinal fluid and a normal ventriculogram. At postmortem examination she was found to have plastic syphilitic meningitis around the optic chiasm and a small gumma of the right parietal lobe.

Hausman feels that the series is much too small on which to base sweeping conclusions but suggests the urgent necessity for considering the presence of optochiasmatic arachnoiditis in all patients who present the clinical syndrome exhibited by his 3 successfully treated patients.

Sutherland-Campbell<sup>156</sup> presents a detailed discussion of the treatment of primary optic nerve atrophy, with particular reference to the evidence which has accumulated pro and con the use of tryparsamide in the treatment of this condition. After weighing the available evidence, he concludes:

Whatever measures are eventually adopted in the treatment of primary atrophy of the optic nerve, I believe that tryparsamide stands condemned, as in the available literature but 7 reports, with a relatively small total number of cases, are concerned with the treatment of primary atrophy of the optic nerve with tryparsamide without damage to the optic system; and in the discussion of one of the reports, a case was included in which the patient seemed to have been adversely affected by the tryparsamide. Only 3 of the reports indicate there was improved vision in a few cases. In practically all other reports covering the greater preponderance of cases, the harmful effect of tryparsamide in the presence of primary atrophy of the optic nerve is contended and maintained, and it appears that the considered opinion of the majority indicates that the use of tryparsamide in the relatively few cases of tabes or of paresis of the tabetic type in which primary atrophy of the optic nerve occurs is not justified in the light of its dangerous potentialities.

*Charcot Joint.*—Distinguishing between the atrophic and the hypertrophic form of Charcot's hip joint, Conley and Miller<sup>157</sup> feel that the

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156. Sutherland-Campbell, H.: Value of Tryparsamide in the Treatment of Atrophy of the Optic Nerve Due to Syphilis, *Arch. Ophth.* 24:670. (Oct.) 1940.

157. Conley, A. H., and Miller, D. S.: Atrophic Charcot's Hips: Report of Five Cases, *J. Bone & Joint Surg.* 22:638 (July) 1940.

former is probably not nearly so uncommon as it has been thought in the past, since they observed 5 instances of the condition in a large hospital service over a two year period. Surgical intervention was of no assistance in the 1 case in which such treatment was tried and is not advised except in certain isolated cases in which this condition is diagnosed early. The prognosis for recovery, as well as for function of the joint, is poor.

The incidence; symptoms; physical findings; results of neurologic, serologic and roentgenologic examination, and treatment of tabetic arthropathy are analyzed on the basis of 58 cases by Pomeranz and Rothberg.<sup>158</sup> They state:

In the series reported the largest number of cases occurred in the fifth and sixth decades, chiefly in white males. Two instances of this disease in colored females are included.

The knee joint was affected in many cases (38.5 per cent). Multiple involvement occurred in 19 cases and, of these, there were 12 instances of bilateral disease.

Careful roentgenographic examination affords the most reliable means for diagnosis and frequently reveals an unsuspected neuro-arthropathy.

In tabetic arthropathy the neurologic examination is more frequently positive than the serologic tests and is therefore a more accurate guide in diagnosis. In the absence of clinical tabes the diagnosis of tabetic arthropathy depends upon the roentgenographic and serologic findings.

Pain is usually present in tabetic arthropathy and disappears late in the disease.

In our series the blood Wassermann test was positive in 48 per cent of the cases and the spinal fluid abnormal in 43 per cent of the cases. The serologic tests were positive in 50 per cent of the patients with neurologic evidence of tabes.

Much has been written regarding the value of fusion or stabilizing operations in this disease, but the end results, in our experience, hardly justify such optimistic claims.

*Tabes Dorsalis.*—Stein and Wortis<sup>159</sup> have previously described the significance of the sensory dissociation and delay in pain perception which are associated with the peripheral neuropathy of chronic alcoholism. They believe a similar sensory dissociation, delay in pain perception and dysesthesia are also noted in cases of tabes dorsalis. The phenomenon, they think, are not clinically well recognized and their physiologic significance is not widely understood. Their explanation for the delayed pain sense is as follows: The peripheral nerve is composed of groups of fibers which differ in their fundamental characteristics. Touch, position and vibratory sensory impulses are carried by one group of fibers which are myelinated, are relatively large in diameter and transmit impulses at high speed to the posterior columns.

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158. Pomeranz, M. M., and Rothberg, A. S.: Review of Fifty-Eight Cases of Tabetic Arthropathy, *Am. J. Syph., Gonorr. & Ven. Dis.* **25**:103 (Jan.) 1941.

159. Stein, M. H., and Wortis, H.: *Tabes Dorsalis: Evaluation of the Sensory Findings*, *Arch. Neurol. & Psychiat.* **46**:471 (Sept.) 1941.

Pain impulses are transmitted by two sets of fibers, partly by large myelinated fibers, which transmit the impulse at high speed, and partly by nonmyelinated fibers, which transmit the impulse at slow speed, to the spinothalamic tracts. This delayed response may be elicited either by pinprick or by stimulation of the sole of the foot.

The authors examined 18 patients with tabes dorsalis who had sensory dissociation and dysesthesia. In 11 of these patients the dysesthetic response was delayed, and in each of these there was marked delay in pain perception.

Hyndman and Jarvis<sup>160</sup> report the result of chordotomy performed at the level of the second or third thoracic segment on 8 patients because of intractable gastric crises. In all, pain and vomiting were relieved. Although loss of sexual function was permanent and retention of urine and occasional motor weakness were transient, they consider that the benefits from this operation outweigh its disadvantages. They believe that previous attempts at chordotomy have often been unsuccessful partly because the operation was carried out at too low a level and partly because section of the cord was too shallow.

*Dementia Paralytica.*—Herman and Rosenblum<sup>161</sup> call attention to the fact that although dementia paralytica is commonly considered a chronic disease with an insidious onset, it may have an acute onset with a rapidly fatal termination. They point out that the initial symptoms of the acute onset may be delirium, convulsive seizures, catatonic phenomena or an acute confusional state. The type which begins with delirium usually runs a fulminating course, whereas the other three types may either behave likewise or in turn progress into a chronic form.

In the chronic forms the authors note that meningoencephalitic changes are more marked in the frontal, parietal and temporal lobes, whereas in the acute forms all cells of the cortex show variable degrees of involvement. They suggest that the acute symptoms occurring in dementia paralytica may be due to the marked vascular reaction, as shown by the intense perivascular infiltration, and point out that under such circumstances an emergency exists and immediate treatment is imperative.

Since the introduction of fever treatment for dementia paralytica about 2,000 articles have appeared on this subject. In the majority it is almost impossible to determine the exact mental status of the patients before treatment was instituted. In only a few papers have the prognosis and the ultimate results of treatment been related to the

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160. Hyndman, O. R., and Jarvis, F. J.: Gastric Crisis of Tabes Dorsalis: Treatment by Anterior Chorodotomy in Eight Cases, *Arch. Surg.* **40**:997 (May) 1940.

161. Herman, M., and Rosenblum, M. P.: Acute Paresis, *Am. J. Psychiat.* **96**: 1311 (May) 1940.

age of the patient, the duration of the disease and the type of psychosis. Greenhill and Yorshis<sup>162</sup> have attempted to devise a working plan to formulate prognosis and have tried to determine why in some instances response to therapy is poor. They studied 100 patients with dementia paralytica admitted to the Worcester State Hospital, Worcester, Mass., between 1925 and 1938. They summarize as follows:

1. One hundred cases of dementia paralytica treated at the Worcester State Hospital between the years 1925-1938 were studied to determine criteria useful in the prognosis. An inquiry into the cause of failure of one-half to two-thirds of paretics to undergo remission under pyretotherapy was also undertaken.

2. These patients were treated by one of four methods: malaria, standard diathermy, modified diathermy and tryparsamide. Thirty-three per cent of the total group underwent remission.

3. The following criteria are found to be of value in the determination of the prognosis; age of the patient, duration of the paretic process, previous therapy, extent of neurological dysfunction, history of epileptiform seizures, degree of defects in sensorium, tendency toward spontaneous remission, type of psychopathology exhibited, and degree of adjustment of the preparetic personality [Family history, mental endowment, educational level, work adjustment, economic status, psychosexual adjustment, alcoholism, court record and personality traits].

4. Most important prognostic criterion is the degree of adjustment in the preparetic personality. All of the patients with well-integrated personalities prior to the onset of dementia paralytica underwent remission no matter what type of therapy they were given. Only three out of 63 patients with poorly adjusted personalities experienced remission.

5. Of the other criteria, the most significant are the extent of neurological dysfunction, degree of defect in sensorium and type of psychopathology. Patients in the delirious, apathetic and agitated groups had the best prognosis, those in the demented and schizophreniform the worst.

6. There is found to be a strong correlation between the degree of adjustment in the preparetic personality and the other prognostic criteria. Well integrated individuals tended to have milder neurological and sensorium defects, slower progress of symptomatology before therapy, and a tendency to spontaneous remission as well as a better prognosis.

*Treatment of Neurosyphilis.*—Boeters<sup>163</sup> briefly reviews the recent literature on the treatment of dementia paralytica. This contribution is noteworthy chiefly for an extensive bibliography.

Ewalt and Ebaugh<sup>164</sup> have undertaken the long term comparative evaluation of artificially induced fever by mechanical means and inocula-

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162. Greenhill, M. H., and Yorshis, M.: Prognostic Criteria of General Paralysis, *Am. J. Psychiat.* **97**:167 (July) 1940.

163. Boeters, H.: Therapie der progressiven Paralyse, *Fortschr. d. Neurol., Psychiat.* **12**:307 (Sept.) 1940.

164. Ewalt, J. R., and Ebaugh, F. G.: Treatment of Dementia Paralytica: A Five Year Comparative Study of Artificial Fever Therapy and Therapeutic Malaria in Two Hundred and Thirty-Two Cases, *J. A. M. A.* **116**:2474 (May 31) 1941.

tion malaria by the only method which offers any prospect of giving a definitive comparison, i. e., the unselected assignment of alternate patients to one or the other method of treatment. They present the results of a five year study of 232 patients with dementia paralytica, half of whom have been treated with artificial fever and the remainder with inoculation malaria. The follow-up treatment was as nearly identical as could be gained in the face of the vagaries of clinical practice. The authors summarize their results as follows:

The method of therapy with artificial fever has been safer and has been productive of better results. The importance of follow-up care is emphasized. Improvement in the care of patients during malaria therapy and more attention to follow-up medication has improved the results of malaria therapy in our clinic, though these results still remain inferior to the results obtained with artificial fever therapy.

Patients with physical contraindications to therapeutic malaria may in many instances be safely treated with artificial fever therapy. Either method is reasonably efficient if properly managed and if general follow-up treatment and care are adequate.

The serologic responses roughly parallel the clinical results in the two series. Careful, periodic, clinical reëxamination offers the best guide for therapy and gives the most reliable data for evaluation of results.

The Cooperative Clinical Group<sup>165</sup> have analyzed the records of patients with dementia paralytica treated with malaria or artificial fever and summarize their observations as follows:

This study evaluates the clinical and serologic results obtained in paresis with artificial fever as compared with malarial therapy. There were 1,100 patients treated with malaria and 320 treated with artificial fever. Throughout the study the data are presented in terms of degree of involvement of paresis on beginning fever therapy. Patients with "mild paresis" were relatively free of deterioration, and their mental symptoms were usually transitory. Patients classified as having "intermediate paresis" exhibited symptoms of manic excitement, depression or other psychiatric syndromes, in addition to evidence of moderate deterioration. Patients with "severe paresis" gave evidence of advanced deterioration.

*Clinical results.*—1. Under either method of fever therapy the earlier in its course the paresis was treated, the more favorable were the results of therapy.

2. The chances of clinical remission in patients with mild paresis were approximately 1 out of 2; in patients with intermediate paresis, 1 out of 4; and in patients with severe paresis, 1 to 10 out of 100.

3. Clinical responses to either type of fever therapy were similar in patients with mild or intermediate paresis on beginning fever therapy. However, this similarity disappeared when treatment was administered to patients with severe

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165. O'Leary, P. A.; Breutsch, W. L.; Ebaugh, F. G.; Simpson, W. M.; Solomon, H. C.; Warren, S. L.; Vonderlehr, R. A.; Usilton, L. J., and Sollins, I. V.: Malaria and Artificial Fever in the Treatment of Paresis, *Ven. Dis. Inform.* 21:278 (Sept.) 1940.

paresis. In fact, the remission rates for patients with severe paresis treated and observed for the same length of time was 1 out of 100 under malaria, as compared with 10 out of 100 under artificial fever. . . .

5. Approximately 90 percent of the total clinical remissions obtained under either method of therapy occurred by the end of the third year of treatment-observation. The degree of parietic involvement on beginning fever therapy influenced the frequency and the speed of expected remissions. Clinical remissions were obtained 1 to 2 years earlier in patients with mild paresis than in those with intermediate or severe paresis. . . .

7. Once a complete remission had been obtained, the chances of its being maintained under either method of fever therapy were 95 out of 100. In a total of 17 relapses, 15 occurred within 3 years subsequent to the year of remission. Relapses were more frequent in severe paresis than in mild or intermediate.

*Serologic results.*—1. Reversal rates for originally positive spinal fluid and blood reactions increased as the duration of treatment-observation increased. . . .

4. Blood as well as spinal fluid reversal-rates were at least twice as great *with* as *without* the use of auxiliary chemotherapy. Among patients *not* treated with auxiliary chemotherapy 42 percent of all spinal fluid reversals subsequently relapsed, as contrasted with only 24 percent spinal fluid relapses among patients *treated* with auxiliary chemotherapy.

5. Two-thirds of all the relapses from spinal fluid reversal occurred within 1 year following the original reversal. . . .

*Relation of clinical to serologic results.*—1. Reversals of both blood and spinal fluids were associated more than twice as frequently with clinical success as with clinical failure. However, since clinical success was not accompanied by complete reversal (blood and spinal fluids) in 52 percent of cases, it follows that *clinical success was not necessarily dependent upon serologic reversal*.

2. Reversal of the spinal fluid was more important than reversal of the blood in indicating the chances of complete clinical recovery. . . .

*Clinical outcome in terms of duration of intensity of fever.*—The highest percentage of clinical remissions was obtained in patients treated with an average of 69 hours' fever above 101° F. (38.3° C.) of which total fever-time 70 percent was at a level above 105° F. (40.6° C.) with a maximum temperature of 106.9° F. (41.6° C.). Equally good results were obtained in patients treated with an average of 44 hours of fever above 101° F. (38.3° C.) of which total time 57 percent was above 106° F. (41.0° C.) with a maximum temperature of 107° F. (41.7° C.). We are of the opinion that fever administered at levels above 106.5° F. (41.4° C.) is hazardous.

Unfortunately, much of the value of this article, especially in a comparison of patients with so-called "severe" dementia paralytica, is lost because of failure to take into account the all-important factor of duration of symptoms of the disease before the institution of one or another type of fever therapy.

Gerstmann,<sup>166</sup> who worked for many years with Wagner-Jauregg, briefly discusses the indications for fever therapy in syphilis of the central

166. Gerstmann, L.: The Indications for Therapeutic Malaria in the Various<sup>4</sup> Forms of Neurosyphilis, *Ven. Dis. Inform.* 22:277 (Aug.) 1941.

nervous system. He divides his neurosyphilitic patients into two groups: those with interstitial or meningovascular disease, primarily involving mesodermal tissue, and those with parenchymatous disease, primarily involving ectodermal tissue. It is his opinion that fever therapy should be more or less limited to cases in which the ectodermal tissue is primarily involved and that of the various forms of fever therapy, malaria seems to be the most effective.

Kawamura and Ueda<sup>167</sup> propose the utilization of tsutsugamushi fever as a therapeutic measure in cases of dementia paralytica. Altogether 113 patients have been inoculated with a relatively avirulent strain of the rickettsias originally isolated from the Pescadores Islands and maintained through rabbit passage. All inoculations were successful, and there were no fatalities due to treatment. The course of the disease when thus induced was apparently benign. From the data presented, therapeutic efficacy cannot be evaluated. Apparently only 41 of the inoculated persons had dementia paralytica, some of whom also received malaria therapy. In all cases the observation period was short.

Because of inability to secure repeatedly high temperatures and because of the reactions accompanying the use of whole typhoid vaccine, Kulchar and Card<sup>168</sup> have attempted to use a vaccine prepared from the flagella of typhoid bacillus (H antigen). The authors treated 118 patients with this antigen. They summarize by stating:

The use of the typhoid flagellar (H) antigen for the induction of fever provides a method that has a number of advantages. The fever can be produced carefully controlled, and terminated as desired. The relatively slight amount of constitutional reaction accompanying the fever makes the method applicable with safety to many patients who are unable to receive other forms of fever therapy. The symptomatic and serologic improvement obtained compares favorably with the results obtained with other forms of fever therapy.

*Malaria Inoculata.*—Mayne and Young,<sup>169</sup> in a general article on the technic of induced malaria, discuss the transferring of the infection, selection of donors, drawing and preserving of blood, inoculation of patients, prepatent and incubation periods, number of paroxysms, termination of infection and contraindications to malarial therapy.

Of interest in regard to transfer of infection is the following material:

1. In order to overcome the difficulty of shipping infected mosquitoes the authors under aseptic conditions removed and put in sterile sodium

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167. Kawamura, R., and Ueda, M.: Eine neue Therapie der Dementia paralytica. (Zugleich eine Prophylaxe gegen Tsutsugamushi), Klin. Wchnschr. **19**:689 (July 6) 1940.

168. Kulchar, C. V., and Card, J. F.: Divided Doses of Typhoid H Antigen Vaccine in the Treatment of Syphilis, Am. J. Syph., Gonorr. & Ven. Dis. **25**:466 (July) 1941.

169. Mayne, B., and Young, M. D.: The Technic of Induced Malaria as Used in the South Carolina State Hospital, Ven. Dis. Inform. **22**:271 (Aug.) 1941.



citrate solution the salivary glands of mosquitoes. Sporozoites thus prepared have remained infective for at least twenty-six days. Such material was at one time shipped to England and still remained infective. The suspended sporozoite material is injected in the same manner as infected blood.

2. Blood to be used for injection at a later date is citrated and immediately put up in 5 cc. vials. The vials are stored in a refrigerator at 40 F., and, according to the authors, the blood will remain infectious for a maximum of fourteen days. This is especially true if there are numerous parasites present in the blood.

Young and his collaborators<sup>170</sup> were able to effect a change in the time of day at which segmenter peaks and temperature elevations occurred by modifying the external environment of the host. If, for example, the segmenter peaks and the temperature elevation occurred at about 9 a. m., reversal of the daily routine of the patient, so that he remained awake, eating and walking about the ward at night, resulted in occurrence of the malarial paroxysms about 9 p. m.

Young and his associates<sup>171</sup> report the following results of observations made on a total of 420 quartan malarial paroxysms which occurred in Negro patients with dementia paralytica:

Only 102 (24 per cent) of these paroxysms were accompanied by chills.

The average measurements for the total 420 paroxysms were: fever-peak, 104.1° F.; time from 100° F. to fever-peak, 4 hours, 35 minutes; time from fever-peak to the end of the fever, 6 hours, 13 minutes.

The durations of the temperature of 100° F. and above averaged 10 hours, 48 minutes. . . .

The chill seemed to exert a definite influence on the character of the paroxysm. When a chill occurred, the duration of the fever was shorter (1 hour, 16 minutes) due mainly to a shortening of the period when the temperature was rising and the maximal temperature was significantly higher (4.3 standard deviations) than in paroxysms without chills. The greatest proportionate increase in temperature occurred during the chilling period.

For some time it has been the hope of those using therapeutic malaria to obtain a drug that when necessary could be used to interrupt temporarily the malarial paroxysms. Brunsting and Love<sup>172</sup> and Cole and

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170. Young, M. D.; Coatney, G. R., and Stubbs, T. H.: Studies on Induced Quartan Malaria in Negro Paretics: II. The Effect of Modifying the External Conditions, *Am. J. Hyg.* **32**:63 (Nov.) 1940.

171. Young, M. D.; Coatney, G. R., and McLendon, S. B.: Studies on Induced Quartan Malaria in Negro Paretics: III. Measurements of the Paroxysmal Phases, *South. M. J.* **34**:709 (July) 1941.

172. Brunsting, L. A., and Love, W. R.: The Tempering Effect of Sodium Bismuth Thioglycollate (Thio-Bismol) on Therapeutic Malaria, *Proc. Staff Meet., Mayo Clin.* **15**:285 (May 1) 1940.

his co-workers,<sup>173</sup> the two groups apparently working independently, have almost simultaneously described the use of thio-bismol for this purpose. By injecting 0.1 to 0.2 Gm. of the drug intramuscularly, fever may be interrupted for several days. Frequently a tertian infection which has been running a quotidian course reverts to a true tertian cycle. It is emphasized that thio-bismol is not a substitute for quinine in the final termination of malaria, since parasites continue to remain in the blood after the drug has been given. These contributions are of the utmost practical importance to all physicians engaged in the therapy of neurosyphilis.

In the course of a symposium on the problems presented by spontaneously occurring malaria, Clark<sup>174</sup> reviewed the recent research on drug prophylaxis and treatment and came to conclusions which are of interest to those who use inoculation malaria as a therapeutic measure, as well as to those who must deal with the spontaneously occurring disease. He states:

Quinine is still our most important drug because of its clinical effectiveness and almost complete safety coupled with the years' widespread knowledge of its use and dosage. "Atabrin" is the drug of choice where expense need not be considered and where some form of supervision of treatment can be placed in effect.

#### SYPHILIS AND PREGNANCY

Speiser<sup>175</sup> discusses at some length the diagnosis of syphilis during pregnancy, the effect of pregnancy on syphilis, the effect of syphilis on pregnancy, the treatment, the results of treatment and the diagnosis of syphilis in the newborn. From the standpoint of the first factor, the author studied 632 cases and concluded, so far as the history was concerned, that the only reliable bit of information is that of previous antisyphilitic treatment or the knowledge of a syphilitic offspring. In 99.6 per cent of the cases the physical examination failed to reveal any manifestations of syphilis.

Basing their report on examination of the records of 386 women with syphilis who were known to have had 453 pregnancies, Dill and his collaborators<sup>176</sup> present a study of the effects of antenatal antisyphilitic

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173. Cole, H. N., and others: Use of Bismuth (Especially Thio-Bismol) Injections to Manage Course of Therapeutic Malaria, *J. A. M. A.* **115**:422 (Aug. 10) 1940.

174. Clark, H. G.: Review of Recent Research on Drug Prophylaxis and Treatment of Malaria: A Report to the National Malaria Committee, *South. M. J.* **33**:879 (Aug.) 1940.

175. Speiser, M. D.: Syphilis and Pregnancy, *New York State J. Med.* **41**:240 (Feb. 1) 1941.

176. Dill, L. V.; Stander, H. J., and Isenhour, C. E.: An Evaluation of the Effect of Antenatal Antisyphilitic Therapy on Fetal Mortality and on Congenital Syphilis, *Am. J. Obst. & Gynec.* **40**:965 (Dec.) 1940.

therapy on fetal mortality and on the incidence of congenital syphilis. They conclude that syphilis need no longer constitute a major cause of fetal mortality and should not be a frequent disease of the newborn. These things may be accomplished by treatment of the syphilitic mother during pregnancy, and in the authors' series this effect was greatly enhanced by treatment received prior to conception. Likewise, a favorable outcome for the child was made more likely by early institution of treatment for the mother, by the advanced age of the mother's infection and by the fact that she had attained seronegativity.

There was in this series no indication of the association of a definite fetal mortality rate with adequate antenatal therapy. The incidence of toxemia of pregnancy and of hydatidiform mole was definitely greater in women with syphilis than in the nonsyphilitic women in the same service. The authors offer no explanation for this but point out that it is apparently not a treatment effect, since toxemia of pregnancy seems peculiarly likely to develop in a syphilitic woman, treated or untreated.

On the other hand, Peckham,<sup>177</sup> in a careful statistical study of 13,742 consecutive deliveries at the Johns Hopkins Hospital, shows that the incidence of toxemia of pregnancy was actually somewhat lower among 1,302 syphilitic women than among 12,440 nonsyphilitic patients and that antisyphilitic treatment did not increase its incidence.

In reviewing the incidence of syphilis in the Duke Hospital, Durham, N. C., Moseley and his collaborators<sup>178</sup> found, in common with other investigators, that more full term live births occurred in the group of syphilitic mothers who received some antisyphilitic treatment, even if given late in pregnancy and in inadequate amounts, than in the group of syphilitic women who had received no treatment or who had been inadequately treated prior to pregnancy.

#### CONGENITAL SYPHILIS

*Diagnosis.*—Ingraham and his collaborators<sup>179</sup> present a five year follow-up study of 230 offspring of syphilitic mothers for the purpose of determining the accuracy of the diagnostic methods employed for the detection of infantile congenital syphilis in the light of recent advances in serologic and roentgenographic interpretation. Approximately one third of the syphilitic group were known to have died, as compared with

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177. Peckham, C. H.: The Effect of Syphilis and Its Treatment on the Incidence of Toxemia of Pregnancy, *Am. J. Syph., Gonorr. & Ven. Dis.* **25**:280, 1941.

178. Moseley, V.; Callaway, J. L., and Sharpe, J. S.: A Study of the Incidence of Syphilis in Pregnant Women and Some Results of Therapy, *Am. J. Obst. & Gynec.* **39**:990 (June) 1940.

179. Ingraham, N. R., Jr.; Shaffer, B.; Spence, B. E., and Gordon, J. H.: Adequate Diagnosis of Infantile Syphilis, *Arch. Dermat. & Syph.* **43**:323 (Feb.) 1941.

one tenth of the nonsyphilitic group, but the authors found it possible to reexamine approximately 70 per cent of the remaining living children after four to five years.

It is considered significant that no infant was discovered in whom serologic tests and the roentgenographic procedures employed had not been able to establish the diagnosis of syphilis in infancy, if it was present.

The spontaneous remission of clinical symptoms and the disappearance of laboratory evidence of the disease after comparatively little or, at times, no anti-syphilitic treatment may be a relatively frequent occurrence among the syphilitic infants who survive the first few months of their disease. Hyperpyrexia from an intercurrent infection may be one of the factors which bring about this apparent "cure."

Recent advances in the knowledge of interpreting the roentgenogram of the long bones in infancy have greatly increased the value of the procedure as a diagnostic aid for congenital syphilis. Misinterpretation of the roentgenogram, which introduced errors as great as 12 per cent five years ago, is becoming uncommon, largely through a better understanding of (1) the occurrence of rather wide variations in normal metaphysial densities, (2) the effect of prepartal treatment of the mother, with heavy metals in producing opaque shadows in the shafts of the infant's bones and (3) the importance of differentiating the early osteochondritic and periosteal changes developing in the malnourished rachitic infant of 2 to 3 months of age. Other causes of diagnostic error have been infrequent in our experience.

Significant roentgenographic changes as a result of syphilis in an infant with negative serologic reactions of the blood are likewise unusual.

It is suggested that the use of the roentgenogram as a subsidiary diagnostic aid will be found of greatest value when it is reserved for the study of those infants in whom a recent infection of the mother or grossly insufficient amounts of prepartal treatment render the presence of the disease in the offspring most likely.

The quantitative titrated Wassermann test seems to have its greatest value in detecting nonsyphilitic infants with positive serologic reactions at birth. In the present series 74 per cent of the infants presenting positive serologic reactions during the immediate neonatal period (up to fourteen days postnatally) apparently did not have syphilis.

The detection of the syphilitic infant by the use of the quantitative titrated Wassermann test alone is complicated by the facts that, first, the birth of a syphilitic infant in whom the serum reagin titer is significantly greater than that of the mother is apparently an infrequent occurrence; second, the syphilitic as well as the nonsyphilitic infant may occasionally exhibit initially a decreasing titer, and third, a significant rise in the serum reagin content may not occur for from four to eight weeks postnatally.

The most accurate diagnosis of infantile congenital syphilis would still seem to call for a close coordination in the interpretation of serologic reactions of the blood and roentgenographic changes.

What Ingraham and associates suggest may represent the relatively frequent spontaneous cure of congenital syphilis in his series seems to us equally likely to represent erroneous diagnoses of congenital syphilis in normal infants by the now discarded standards in vogue when the infants in question are born.

Evans,<sup>180</sup> working at the Childrens Hospital, Detroit, discusses some of the problems which have come to his attention in the study of routine roentgenograms of the long bones of premature infants and infants in whom syphilis was suspected. He points out that in some instances there may be normal bones on roentgenologic examination of a definitely syphilitic child, roentgenologic changes appearing subsequently, and that in other instances changes due to nutrition and growth may closely simulate syphilitic lesions.

Senear<sup>181</sup> reviews and discusses briefly the more important papers devoted to the diagnosis of congenital syphilis in infancy which have appeared in recent years.

*Interstitial Keratitis.*—In an excellent article, Klauder and Vandoren<sup>182</sup> have analyzed the results of treatment of 532 patients with interstitial keratitis. The authors' summary and conclusions cannot be improved:

*Summary and Conclusions.*—A report is made of an analysis of 532 patients who were treated or observed for at least 1 year.

Seventy-three per cent of the patients were white, 27 per cent were Negroes. Sixty per cent were females. The median age at onset was 12 years for females, and 13 years for males.

Thirty per cent of patients with inactive interstitial keratitis previously treated had a negative serologic reaction of the blood; 2.5 per cent of patients with active interstitial keratitis who were untreated had a negative reaction.

In 532 patients other syphilitic manifestations were incident in varying degrees, as follows: Hutchinsonian teeth, 40 per cent; bone and joint involvement, 35 per cent; labyrinthine disease, 10 per cent; chorioretinitis, 8 per cent; neurosyphilis (symptomatic and asymptomatic), 8 per cent; paresis and taboparesis, 0.4 per cent.

In 42 per cent of patients both eyes were involved either simultaneously or within 1 month of each other. The percentage with second eye involvement increased slowly to the tenth year. At this time the second eye had become involved in 79 per cent.

The effect of different schemes of treatment on final visual acuity, with or without refraction, was graphically represented. Different schemes of treatment comprised routine (more than 20 injections of an arsenical or less than 20 injections in conjunction with a heavy metal), routine with iodides, routine with fever (malaria, mechanical fever therapy, or vaccines intravenously), and routine with iodides and fever. Treatment was also classified as continuous, intermittent, and irregular.

It appeared that treatment administered in the inactive stage of interstitial keratitis was of limited value in improving visual acuity.

The importance of employing at least 20 injections of an arsenical in the active stage of the disease was emphasized. Arsphenamine and neoarsphenamine obtained approximately the same results.

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180. Evans, W. A., Jr.: Syphilis of Bones in Infancy: Possible Errors in Roentgen Diagnosis, *J. A. M. A.* **115**:197 (July 20) 1940.

181. Senear, F. E.: Diagnosis and Treatment of Syphilis in Infancy and Teen Age, *Illinois M. J.* **78**:448 (Nov.) 1940.

182. Klauder, J. V., and Vandoren, E.: Interstitial Keratitis: Standardization of Treatment, *Ven. Dis. Inform.* **22**:307 (Sept.) 1941.

The administration of iodides unfavorably influenced final visual acuity in both active and inactive interstitial keratitis.

The superiority of one plan of treatment over another involved an increase in the proportion of patients with excellent vision following treatment and not a decrease in the proportion whose sight remained poor.

Routine therapy supplemented with fever therapy was superior to other forms of treatment in preventing relapse. Of 55 patients thus treated only one had a relapse. Relapses after other types of treatment ranged from 13 to 18 per cent. Relapse was more frequent in patients treated with less than 20 injections of an arsenical than in patients treated with more than 20 injections.

Continuous treatment was superior to intermittent or irregular treatment only insofar as concerned final visual acuity of the poorer eye, and in causing less poor visual acuity or blindness.

Best results were obtained in patients with active interstitial keratitis who were treated with an arsenical combined with the use of a heavy metal and fever therapy. This treatment resulted in the following final visual acuity (total eyes): Excellent (20/30 to 20/20), 51 per cent; good (20/50 to 20/40), 17 per cent; fair (20/200 to 20/70), 22 per cent; poor (less than 20/200) and blind, 10 per cent. This compares with the visual acuity (total eyes) of untreated patients (control group) as follows: Excellent, 24 per cent; good 27 per cent; fair, 37 per cent; poor and blind, 12 per cent.

In the course of a general review of the etiologic role played by riboflavin deficiency in various types of ocular disease, Johnson and Eckardt<sup>183</sup> have been unsuccessful in treating syphilitic interstitial keratitis with riboflavin. The authors emphasize the following points:

Interstitial keratitis with "fine interlacing and anastomosing vessels located just beneath the epithelium" and with "the posterior membrane covered with a fine vascular plexus" represents a type of corneal disease with which we are not familiar, and a dietary deficiency may coexist. For this type of pathologic process, the improvement following the use of riboflavin is reported as very promising.

*Heart Disease in Congenital Syphilis.*—Koons and Kissane<sup>184</sup> have reviewed the worthwhile articles pertaining to the incidence of heart disease in children with congenital syphilis and have studied the problem in two respects. They examined a group of 100 congenitally syphilitic children between the ages of 2 and 10 years; of these, only 1 child had heart disease (rheumatic mitral stenosis). Conversely, of 334 children with known heart disease, only 1 had congenital syphilis. They agree, therefore, that the heart and great vessels are rarely if ever affected by congenital syphilis.

*Intelligence and Congenital Syphilis.*—Jenkins, Brown and Cisler<sup>185</sup> have reviewed the literature relating to the association of feeble-minded-

183. Johnson, L. V., and Eckardt, R. E.: Ocular Conditions Associated with Clinical Riboflavin Deficiency, *Arch. Ophth.* **24**:1001 (Nov.) 1940.

184. Koons, R. A., and Kissane, R. W.: Incidence of Heart Disease in Children with Syphilis, *Urol. & Cutan. Rev.* **44**:673 (Oct.) 1940.

185. Jenkins, R. L.; Brown, A. W., and Cisler, L. E.: Influence of Syphilis on Intelligence of Children, *Am. J. Dis. Child.* **60**:341 (Aug.) 1940.

ness and congenital syphilis. They examined 141 feeble-minded children, and their conclusions are in agreement with those of Lurie and his co-workers,<sup>186</sup> who examined 1,850 children presenting behavior problems. Both groups of investigators conclude that congenital syphilis does not contribute to feeble-mindedness unless the central nervous system is involved, usually by juvenile dementia paralytica.

*Hereditary Ectodermal Dysplasia of the Anhidrotic Type.*—Kaalund-Jørgensen and Christensen<sup>187</sup> find, after reviewing the literature pertaining to hereditary ectodermal dysplasia of the anhidrotic type, that in addition to the numerous cases reported from India, there are 58 indubitable cases reported from the European countries; to these the authors add detailed reports of the cases of 2 brothers who presented typical instances of the syndrome. Sunderman<sup>188</sup> also reports 3 additional cases occurring in one family. Both reports describe the salient features of the disease as follows: the absence of sweat glands and at times of lacrimal glands; the growth of scanty, fine, lanugo type of hair, and the total absence or incomplete development of teeth.

In discussing the etiology of the condition, the authors bring out that the characteristic appearance—the saddle nose, purulent rhinitis and conical incisors (though entirely different from the typical Hutchinson teeth) might suggest congenital syphilis, and several patients have in fact been mistakenly treated under that diagnosis. The condition has nothing whatever to do with that disease, however, and in none of the reported cases has there been evidence on which to base a diagnosis of syphilis.

#### SYPHILIS AND OTHER DISEASES

*Syphilis and Diabetes.*—In view of the suggestions which have been made from time to time regarding syphilis as an etiologic factor in diabetes, McDaniel, Marks and Joslin<sup>189</sup> state:

A careful study of 258 patients with diabetes and with syphilis from a total of 15,095 patients with diabetes has been presented. All have met specific criteria for diagnosis.

A review of cases presented in the literature as instances of diabetes due to syphilis shows that practically all of them fail to satisfy the criteria we have set as being essential for proof of this relationship.

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186. Lurie, L. A.; Greenebaum, J. V., and Brandes, E. B.: Syphilis as Factor in Behavior Disorders of Children, *Urol. & Cutan. Rev.* **45**:108 (Feb.) 1941.

187. Kaalund-Jørgensen, O., and Christensen, J. F.: Congenital Ectodermal Dysplasia of the Anhidrotic Type, *Acta dermat.-venereol.* **22**:1 (Feb.) 1941.

188. Sunderman, F. W.: Persons Lacking Sweat Glands: Hereditary Ectodermal Dysplasia of the Anhidrotic Type, *Arch. Int. Med.* **67**:846 (April) 1941.

189. McDaniel, L. T.; Marks, H. M., and Joslin, E. P.: Diabetes Mellitus and Syphilis: A Study of Two Hundred and Fifty-Eight Cases, *Arch. Int. Med.* **66**:1011 (Nov.) 1940.

The chief factors in the causation of diabetes (positive heredity history of diabetes, the state of being overweight and the age at onset of diabetes) have been shown to be the same for diabetic patients with syphilis as for diabetic patients without syphilis.

If "syphilitic diabetes" occurs, theoretically it would most likely be a late manifestation of syphilis occurring in older persons, except in patients with congenital syphilis, in whom diabetes is uncommon.

Part of the evidence against the relationship of the two diseases is the fact that there is a marked difference between the sexes in the duration of syphilis before the onset of diabetes.

A diabetic patient with syphilis may be given antisyphilitic treatment with the same considerations given to any patient concerning the plan of treatment.

To be certain that antisyphilitic treatment has improved or cured diabetes, a case must be followed for years and the condition checked with dextrose tolerance tests.

In this series of 258 patients there has not been a single instance of cure of diabetes brought out by optimum antisyphilitic treatment.

On the average, a patient with syphilis and diabetes does not appear to have any type of diabetes different from that of the usual patient of the same age.

We have not been able to recognize the characteristics of such a clinical entity as "syphilitic diabetes."

Williams<sup>190</sup> approaches the problem from the clinical and pathologic point of view and states:

In a series of 1,000 proved standardized cases of diabetes mellitus, syphilis (active or latent) was demonstrated and treated in 17 instances. This ratio is in accord with the experience of other observers and conforms to the incidence of the disease in the general population.

Review of the 4,800 necropsies which have been performed at the Strong Memorial Hospital, Rochester, N. Y., failed to reveal a single case of syphilitic pancreatitis, excluding congenital syphilis. There is no evidence then, either directly or indirectly, for a causal relation between syphilis and diabetes.

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190. Williams, J. R.: Syphilis and Diabetes Mellitus: A Critical Study of Their Relation to Each Other in One Thousand Cases of Diabetes Mellitus, New York State J. Med. 41:252 (Feb. 1) 1941.



## News and Comment

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**Fellowships for Research in Nutrition.**—Scientific attack on problems of the American diet was furthered recently by a series of fellowships established by Swift and Company for research in nutrition to aid the federal government in its long range national nutrition program.

The fellowships provide for special research to be undertaken in laboratories of universities and medical schools with funds which the company has set aside as grants in aid beginning Nov. 1, 1941. The fellowships will be for one year but may be renewed if the project warrants.

Any fundamental study of the nutritive properties of foods or the application of such information to improvement of the American diet and health will be eligible for consideration for a grant, according to Dr. R. C. Newton, vice president in charge of the company's research laboratories, who will coordinate the program.

## Book Reviews

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**The Roentgen Density of the Cystine Calculus: A Roentgenographic and Experimental Study, Including a Comparison with More Common Uroliths.** By Axel Renander, Chief, Roentgen Department, Centrallasarettet, Västerås, Sweden. Translated from the Swedish by Catherine Djurklou. *Acta radiol. supp.* XLI. Price, 15 kronor. Pp. 147, with 66 figures and 22 tables. Stockholm: P. A. Norstedt & Söner, 1941.

In the general opinion of radiologists and urologists and according to current expressions of opinion in textbooks, cystine calculi are difficult to visualize on roentgenologic examination. In a review of 37 cases of cystinuria reported in Sweden, the author found that the condition in 27 was complicated by the formation of calculi. In 18 of the 27 cases a roentgenologic study had been made prior to operation, and in 15 of these 18 cases available cystine calculi were examined roentgenographically with respect to structure and investigated photometrically for the purpose of studying their roentgen density.

In the 18 cases 13 patients were men and 5 were women. The first symptoms of lithiasis usually appeared between the ages of 20 and 25 years, although the age at onset varied from 1½ to 64 years. As a rule, the patient had stone symptoms for four or five years before a diagnosis of cystinuria was made. The lithiasis was bilateral in 4 cases. In 1 case it was observed that new cystine calculi up to the size of almonds developed within a period of five months. The largest cystine calculus weighed 50.2 Gm. and originated in the bladder. One large ureteral stone weighed 40.7 Gm. Large vesical and coral stones were observed with remarkable frequency in children.

As a rule the cystine calculi are nearly pure, having an ash content of less than 1 or 2 per cent, but in the vesical calculi layers containing as much as 2 or 3 per cent are observed. Phosphate stones were found in 2 cases of cystinuria. The morphologic structure of cystine calculi was generally more or less granularly homogeneous. Sometimes in the periphery there were seen concentric lamellations and radiating bands.

In 15 of the 18 cases the stones gave good shadows in the roentgenograms made in vivo. This remark applies to pure cystine stones, as well as to the small ones. In 3 cases small stones were not distinguishable in the roentgenograms, probably because of overlying intestinal contents and because of their vacuolated structure.

The roentgen density of the cystine calculus increases with the ash content, decreases somewhat with the wavelength and drops in air from 3.8 at 50 kilovolts to 3.2, at 90 kilovolts. Determination of the roentgen density of the cystine calculus in water, employing a secondary diaphragm and intensifying screens and in general the same conditions as those which apply in a roentgen practice, gave an average value of 2.7, or 30 per cent lower than in air. No real variation in the roentgen density of the cystine calculi could be observed at the voltages used in practice (50 to 64 kilovolts).

Photometric examination of other urinary concretions showed a roentgen density in air of 1.1 for the uric acid stone, 4.9 for the calcium oxalate stone, 5.1 for the ammonium magnesium phosphate stone and 7.6 for the calcium diphosphate stone, all in relation to water. A roentgen density in water of 3.2 was obtained for the ammonium magnesium phosphate stone and of 5.7 for the calcium diphosphate stone.

While the book is, for the most part, a technical treatise on roentgen and photometric density as related to cystine calculi, there is an excellent clinical

summary of the 18 case reports, with roentgenograms and photometric charts of the specimens. Practically, it may be said that even when not mixed with inorganic substances the cystine calculus casts a good, and in many cases a dense, roentgen shadow. In exceptional cases small cystine stones may escape detection.

**Cardiac Classics. A Collection of Classic Works on the Heart and Circulation, with Comprehensive Biographic Accounts of the Authors (Fifty-five contributions by 51 authors).** Edited by Frederick Willius, M.D., Chief of the Section of Cardiology, the Mayo Clinic; Professor of Medicine, the Mayo Foundation for Medical Education and Research, the Graduate School, the University of Minnesota; and Thomas E. Keys, M.A., Reference Librarian, the Mayo Clinic, formerly Carnegie Fellow, the Graduate Library School, University of Chicago. Price, \$10. Pp. 558, with illustrations. St. Louis: C. V. Mosby Company, 1941.

This volume contains a well chosen collection of the classic contributions to medical science on which present day knowledge of heart disease is based. It begins most appropriately with Harvey's "An Anatomical Disquisition on the Motion of the Heart and Blood in Animals." This is just as it should be, for with this work of Harvey's begins the history of the study of heart disease, and it is on the foundation furnished by this work that most of the knowledge of heart disease is based. There follows a series of fifty-one articles by the men who, from Harvey to James B. Herrick, have contributed the most important building blocks which go to form the present structure.

Unlike some personally conducted tours, during which only a glimpse is given of the points of interest, in this collection the articles are reprinted in their entirety. This adds a great deal to the value of the volume. It has always seemed a bit presumptuous for any one to choose for the reader just what should be presented to him and what should be omitted in the reproduction of such important earlier writings.

Each article is accompanied by a historical sketch of the writer. This is not the "comprehensive biographic account" stipulated in the title. In most cases it is adequate but just barely so.

And again as in personally conducted tours, it may be said that the reader would experience much greater pleasure if he found these works for himself, and also, that much of interest has been omitted. But in this tour of the history of heart disease, the reader is given access to material, much of which he could find only with difficulty, and some of which would be almost inaccessible, especially in a translated form. As in tours of historic places, he not only can return again and again to points of interest by himself, but he will be stimulated to explore for himself the writings of earlier men. Not only will he find a medical literature which it is frequently a great pleasure to read because of its diction and its wisdom, but he will come to look on his medical grandfathers with a new respect and will return to his own work with a "humble and a contrite heart" when he reflects how much they accomplished, with so little in the way of aid from previous stores of knowledge and instruments, by observation and by quietly thinking about what they had observed.

This well chosen collection of classic works can be recommended to all who are interested in other fields of medicine as well as in heart disease.

**Operative Surgery, Including Anesthesia, Pre- and Postoperative Treatment, Principles of Surgical Technic, Blood Transfusion, and Abdominal Surgery.** Edited by Frederic W. Bancroft. Price, \$10. Pp. xix + 1,102, with illustrations. New York: D. Appleton-Century Company, Inc., 1941.

Amazingly enough the title of this book is not sufficiently inclusive, because in addition to the subjects mentioned there are presented sections on surgery of the mouth and of the esophagus. Perhaps the explanation for the inclusion of these subjects in a volume the purpose of which "is to present surgical treat-

ment of abdominal diseases . . ." lies in their close embryologic relation to the gastrointestinal tract. Actually, the book consists of a collection of monographs on the subjects already mentioned and on the surgical management of lesions of the gastrointestinal tract, the biliary tract, the liver, the pancreas and the spleen and of peritonitis and peritoneal abscesses. One chapter is devoted to the significance of gastroscopy and another to diets for patients operated on for abdominal conditions. With few exceptions the collaborators who have written these various sections are distinguished surgeons well recognized for their contributions in these respective fields.

Whereas a volume of this character obviously contains much informative and instructive material, occasional contradictions, important omissions and unnecessary repetitions are difficult to avoid and require strict editing and close adherence of the contributors to the subject. In this respect the efforts have been rather mediocre. Perhaps one of the most obvious examples of the last-named defect is the description with illustrations (many of which are the same) of the Nather-Ochsner method of drainage of a subdiaphragmatic abscess in three different sections (section VIII, pp. 498-502; section XIII, pp. 790-794, and section XVII, pp. 957-958). Other defects which are difficult to avoid in this type of book are the variations in the methods and caliber of the expositions and the disputable importance given certain methods or surgical procedures which may be the respective authors' contributions. Thus, while the anatomic relations of the organs concerned are described and illustrated in great detail in some chapters, this phase of the subject is completely omitted in others. In the chapter on surgery of the spleen the "authors'" method of splenectomy is such a slight modification of Wilkie's method that the necessity of 4 extra pages of description and illustration appears incommensurate with its significance.

Aside from these deficiencies, however, the book is generally satisfactory. Some of the chapters attain a high standard of excellence. Perhaps the greatest value of the book lies in the ready availability of much informative, authoritative and practical material.

**Chinese Lessons to Western Medicine.** By I. Snapper, M.D., Professor of Medicine, Peiping Union Medical College. Price, \$5.50. Pp. X + 380, with 132 illustrations. New York: Interscience Publishers, Inc., 1941.

This book is particularly interesting because it so well points out how much valuable information can be obtained in medicine by applying new methods to old problems.

Clearly the medical clinic at Peiping Union Medical College is as up-to-date and modern as can be. The records, roentgenograms, clinical charts, photographs and laboratory data in use there prove this and compare favorably in their modernity with any in America. On the other hand, the diseases which are encountered are mostly as old as China itself, handed on from one generation to the next, perhaps modified by superstition, constitutional peculiarities, eating habits, education, available food or even by the vicissitudes of war and famine.

That all these factors have influenced the clinical picture of disease during the course of time is strongly suggested by comparing the description of what the author has observed there with what most physicians encountered in this country in similar fields. Dr. Benjamin Waterhouse had this same thought in mind more than a hundred and fifty years ago when he voiced the suspicion that any disease appearing in New England might evolve with time into something quite different than it had seemed to be in old England.

Dr. Snapper's book makes delightful reading for the internist inclined to play the philosopher. As one studies it one develops a sense of pride in the realization that other things than Standard Oil and Ford cars are helpful to an old civilization like that of China and a sense of humility in perceiving that the infectious or parasitic diseases, the disorders of the liver, the diseases of the cardiovascular and renal systems and the anemias when carefully studied in China all have new lessons for those who practice internal medicine in this country.

**The 1941 Year Book of Pathology and Immunology.** Edited by Howard T. Karsner, M.D., Professor of Pathology, Director of the Institute of Pathology, Western Reserve University, Cleveland; and Sanford B. Hooker, M.D., Professor of Immunology, Boston University School of Medicine; member of the Evans Memorial for Clinical Research and Preventive Medicine and Immunologist, Massachusetts Memorial Hospitals. Price, \$3. Pp. 623, with illustrations. Chicago: The Year Book Publishers, Inc., 1941.

The physician in general practice or the one in some special practice finds little time in which to keep up his knowledge of the basic sciences on which his daily work is founded and with which it is essential that he shall be conversant. This volume is an especially well edited review of the year's more significant advances in pathology and immunology. It is comprehensive but still concise. It begins with a summary of Dr. Moon's work on shock, prefaced by Dr. Moon himself and included in the chapter on general pathology. The chapter on tumor presents a review of recent work on tumors and their genesis and is followed by chapters on the various contributions to pathology appearing during the year, classified under the different body systems, as renal, cardiovascular, etc.

The section on immunology includes not only material concerning diseases caused by bacteria, viruses and the higher parasites but reviews of chemotherapy, anaphylaxis, allergy and the important recent work on blood groups.

It would be an extraordinary person who could keep up his knowledge of the work in these basic fields and, at the same time, keep up with the literature in his own field without the aid of some such book. And this particular book can be recommended without qualifications.

**Pinel.** By Dr. Juan Ramón Beltran. Pp. 64, with 1 illustration. Buenos Aires: Privately printed, Ferrari Hnos, 1940.

Those with an interest in medical history will be glad to become acquainted with Dr. Philippe Pinel through this small monograph. Pinel was a distinguished pioneer in the field of mental disease and had much to do with reforming the care of the mentally ill in France during the early part of the nineteenth century. His story is pleasantly told here, and his work is properly fitted into place by considering what psychiatry was before his time, how he influenced and reformed it and what, essentially, were his philosophy and ideals.

This reprint gives an attractive idea of how medical history is respected by our colleagues in South America.

**Viruskrankheiten des Menschen.** By Prof. Dr. Med. E. Haagen. Price, 10 marks. Pp. 162. Leipzig: Theodor Steinkopff, 1941.

This booklet, the thirtieth in a series on the practice of medicine, is divided into the following eight parts: I. Exanthematous Diseases; II. Vesicular Diseases; III. Pustular Diseases; IV. Diseases of the Respiratory System; V. Diseases of the Nervous System; VI. Septicemic Diseases; VII. Diseases of Other Location, and VIII. Rickettsial Diseases and Trachoma.

In this manner, the author succeeds well in covering his field. His clear style and many authoritative references make the volume well suited for the student or the practitioner who has a good reading knowledge of German.

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## RELATION OF CARDIAC LESIONS TO THE CLINICAL COURSE OF RHEUMATIC FEVER

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NEW YORK

Most investigators are agreed that observed differences in the frequency of the myocardial Aschoff body in rheumatic heart disease are the result of the transient nature of the lesion. Aschoff<sup>1</sup> recognized this relation, and others<sup>2</sup> have observed the disappearance of the Aschoff body after the disappearance of symptoms of rheumatic fever.

More recently, Gross and Ehrlich<sup>3</sup> have described the development of the Aschoff body and have attempted to correlate the changes with the clinical course of the disease. They found that the lesion was common in cases in which the infection showed "clinical or anatomical evidence of activity" but infrequent when the disease pursued a chronic course.

At the present time the Aschoff body is almost universally accepted as evidence of existing rheumatic disease, but the terms active infection and activity are ill defined. Active infection has been assumed to occur with changes varying from leukocytosis or persistent tachycardia to typical migratory polyarthritides and with lesions as diverse as scattered groups of lymphocytes in a valve leaflet and typical Aschoff bodies.

From 2,300 consecutive cases in which autopsy was done at the New York Hospital were selected all those in which there was, on the one hand, clinical evidence of rheumatic fever, that is, a definite history of migratory polyarthritides, chorea or pains about joints, sometimes designated as growing pains, or, on the other hand, verrucae, acute pericarditis or chronic endocarditis. Cases were included in the series only if one or more of these lesions were present. Ninety-eight cases

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From the Department of Pathology of Cornell University Medical College and the New York Hospital.

1. Aschoff, L.: Zur Myocarditisfrage, *Verhandl. d. deutsch. path. Gesellsch.* **8**:46, 1904.

2. Talalajew, W. T.: Der akute Rheumatismus, *Klin. Wchnschr.* **8**:124, 1929.  
Klinge, F.: Der Rheumatismus, *Ergebn. d. allg. Path. u. path. Anat.* **27**:1, 1933.

3. Gross, L., and Ehrlich, J. C.: Studies on the Myocardial Aschoff Body, *Am. J. Path.* **10**:467 and 489, 1934.

fulfilled this criterion. Aschoff bodies were accepted as unequivocal evidence of the disease, and no case in which these lesions were present was excluded, even if a history of the named symptoms could not be obtained. In 3 cases in which acute or chronic endocarditis was evident Aschoff bodies were found, although there was no history of rheumatic fever. These cases will be considered separately.

The number of heart sections examined for microscopic lesions varied in different cases from 2 to 6, with an average of 3 sections per case.

Of the 98 cases in which both clinical evidence of rheumatic fever and lesions of the endocardium or the pericardium were present, there were Aschoff bodies in the myocardium in 28 (28.5 per cent). The cases fell into two groups, depending on whether an attack of polyarthritis had occurred within five months of the time of death. There was a record of chorea in 9 cases, and the interval between an attack and death varied between one and a half and thirty-six years. Chorea was not included in this distinction, because no deaths occurred within five months of an attack. Vague joint and growing pains were not included because these symptoms were frequently so indefinite that time relations could not be determined. The following tabulation indicates the results of such grouping:

Interval Between Last Attack of Polyarthritis and Death	Total No. of Cases	—Occurrence of Aschoff Bodies—	
		No. of Cases	Percentage of Cases
5 months or less.....	27	27	100
More than 5 months.....	71	1	1.4
Total .....	98	28	28.5

In cases in which Aschoff bodies were found the longest period that had elapsed between the last attack of polyarthritis and death was five months. This period was four and five months, respectively, in only 2 cases, and in the case in which the interval was five months some of the Aschoff bodies were recognized with difficulty because they were masked by interstitial fibrosis and in places completely obliterated. Similar fibrosis with no recognizable Aschoff bodies was observed in many of the sections from hearts of patients who died more than five months after the last attack of polyarthritis.

In 1 case in which Aschoff bodies were present the interval between the last attack of polyarthritis and death was more than five months. The patient in this case was a 57 year old man who at autopsy showed advanced mitral stenosis and fresh verrucae. The last attack of polyarthritis occurred at the age of 20 years. His heart began to compensate at the age of 45, and at this time he complained of fleeting joint

pains, which continued until death. Five months before death he was seen in the cardiac clinic, at which time he complained of joint pains and “pains all over the body.”

In 3 cases in which Aschoff bodies were recognized the patients gave no history of polyarthrititis, chorea, joint pains or growing pains at any time. The first patient was a 23 year old man who at autopsy showed advanced mitral and aortic stenosis, fresh verrucae and fresh pericarditis. He gave a history of frequently repeated sore throat with fever but no joint symptoms or chorea. He died of cardiac failure two weeks after he contracted pharyngitis caused by a beta hemolytic streptococcus.

The second patient was a 25 year old man with mitral stenosis and fresh verrucae recognized at autopsy. He gave no history of arthritis or chorea and died of lobar pneumonia.

The third patient was a 25 year old woman who had fresh verrucae but no evidence of chronic endocarditis. She died of fulminant broncho-pneumonia caused by a hemolytic streptococcus and meningoencephalitis.

Of 31 cases in which Aschoff bodies were recognized, an attack of polyarthrititis had occurred in 27 within five months before death, vague joint pains in 1 and sore throat in 1, and in 2 no symptoms suggestive of rheumatic infection had been recorded. Aschoff bodies were found in only 4 (5.4 per cent) of 74 cases in which there was evidence of endocarditis or pericarditis but no history of recent polyarthrititis.

A part of this series of cases had previously been studied by Delavett,<sup>4</sup> who divided them into groups according to the age of the patient at the time of death. He found that of those cases in which there was evidence of endocarditis and a history of rheumatic fever Aschoff bodies were present in the myocardium in 87 per cent in which death occurred between the ages of a few months and 9 years, in 63 per cent in which death occurred between the ages of 10 and 19 years and in only 10 per cent in which death occurred after the age of 20. The following tabulation shows this age distribution in the present series.

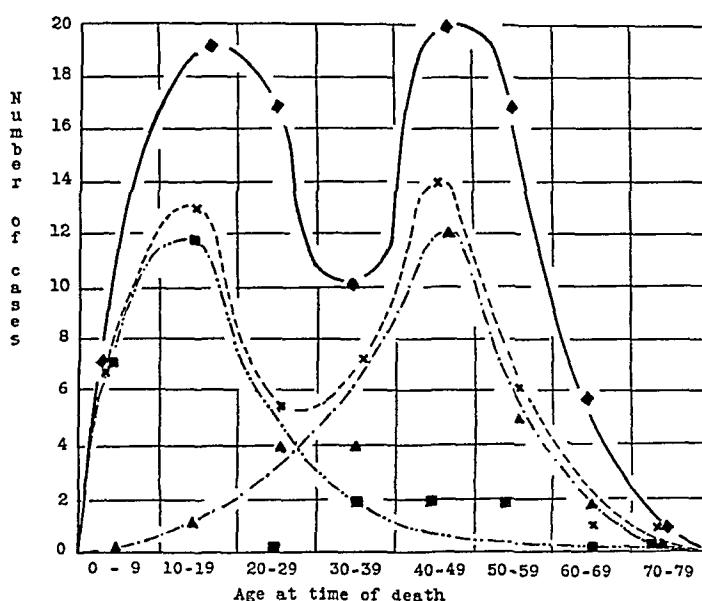
Age, Yr.	No. of Cases	—Occurrence of Aschoff Bodies—	
		No. of Cases	Percentage of Cases
0-9 .....	7	7	100
10-19.....	19	12	64
20-29.....	17	1	6
30-39.....	11	2	18
40-49.....	20	2	10
50-59.....	17	2	11
60-69.....	6	1	17
70-79.....	1	0	0

4. Delavett, A.: Unpublished data.



In the first decade of life Aschoff bodies were found in all cases of endocarditis or pericarditis in which there was a history of rheumatic fever. In the second decade Aschoff bodies were present in 64 per cent of cases but in only 11 per cent of cases in later decades.

Fresh verrucae and fibrinous pericarditis have been accepted by many investigators as anatomic evidence of active rheumatic infection. In this series, of 27 cases in which recent attacks of polyarthrititis had occurred, Aschoff bodies were present in all cases, verrucae in 89 per cent and pericarditis in 60 per cent. Of 71 cases in which there was no record of a recent attack of polyarthrititis, Aschoff bodies occurred in 1.4 per cent, verrucae in 5.5 per cent and pericarditis in 4.5 per cent. No con-



The distribution, according to age, of cardiac failure and the occurrence of Aschoff bodies in 98 cases in which there were both clinical symptoms of rheumatic fever and evidence either of endocarditis or of pericarditis at autopsy. The symbols bear the following significance: diamond, total number of deaths from all causes; cross, total number of deaths from cardiac failure; square, number of deaths from cardiac failure with Aschoff bodies recognized at autopsy, and triangle, number of deaths from cardiac failure without recognition of Aschoff bodies at autopsy.

stant relation between the clinical symptoms and these different combinations of lesions could be found.

The series of 98 cases in which both clinical symptoms of rheumatic fever and endocarditis or pericarditis were present was analyzed on the basis of age and the cause of death. The following tabulation shows the distribution of cases according to the cause of death and the occurrence of Aschoff bodies, and the figure gives the distribution in relation

to age at the time of death and the incidence of cardiac failure and Aschoff bodies:

Cause of Death	No. of Cases	Percentage of Cases
Cardiac failure (total).....	55	56
Cardiac failure with Aschoff bodies.....	25	26
Cardiac failure without Aschoff bodies.....	30	31
Subacute bacterial endocarditis.....	18	19
Other causes .....	25	26

The bimodal form of the curve (figure) representing deaths from cardiac failure is obviously dependent on the curves representing deaths from cardiac failure with Aschoff bodies, on the one hand, and without Aschoff bodies, on the other, rather than on the chance distribution of deaths due to other causes. Death from cardiac failure is apparently of two types, affecting two groups of persons which are in great part widely separated with respect to age, though they show a slight tendency to overlap. Those cases in which Aschoff bodies occur fall in the first three decades and those in which these lesions are absent fall chiefly in the age group of 40 to 60 years. It is noteworthy that since the presence of Aschoff bodies agrees to within 90 per cent with the presence of polyarthritis, the essential form of these curves would not be altered if one or the other of these criteria were used.

The lesions of the mitral valve in the 98 cases in this series were divided into four grades, depending on the degree of damage to the valves. In grade I were placed valves which showed scant thickening or verrucae without evidence of thickening. In grade II were included all valves with moderate thickening but no evidence of stenosis. Grades III and IV comprised definitely stenotic valves, the former including thickened rigid valves and the latter the more advanced lesions, which were the so-called "fish-mouth," or "button-hole," valves. The same type of arbitrary classification was applied to lesions of the aortic valve, and for each case the maximum damage to the aortic or the mitral valve was recorded (the mitral valve was damaged in over 85 per cent of cases).

The following tabulation shows by decades the distribution of different grades of valvular damage:

Age, Yr.	Grade of Valvular Damage			
	I	II	III	IV
0-9 .....	4	2	1	0
10-19 .....	3	13	3	0
20-29 .....	3	4	5	6
30-39 .....	1	2	2	5
40-49 .....	1	3	6	10
50-59 .....	1	2	10	3
60-69 .....	1	2	4	0
70-79 .....	1	0	0	0
Total number of cases.....	15	28	31	24

The minor grades of valvular deformity (I and II) preponderate in the first three decades. The advanced degrees of deformity tend to occur later in life, and lesions of grade IV do not appear during the first two decades.

The following tabulation shows the relation between cause of death and the degree of valvular damage:

Cause of Death	Grade of Valvular Damage							
	I		II		III		IV	
	No. of Cases	% of Cases	No. of Cases	% of Cases	No. of Cases	% of Cases	No. of Cases	% of Cases
Cardiac failure with Aschoff bodies .....	10	66	10	34	6	20	0	0
Cardiac failure with no Aschoff bodies .....	1	7	2	8	9	28	19	78
Other causes.....	4	27	16	58	16	52	5	22
Total number of cases.....	15		28		31		24	

On the one hand, the incidence of deaths from cardiac failure with Aschoff bodies in the myocardium decreases as valvular deformity increases. On the other hand, the incidence of deaths from cardiac failure without Aschoff bodies increases as deformity increases. Expressed differently, in slightly more than three fourths of all cases in which death was due to cardiac failure and in which Aschoff bodies were present the lesions of the valves were of the least deforming types (grades I and II), while in an even greater proportion of cases in which the death was due to cardiac failure and there was no evidence of Aschoff bodies the greatest deformity of the valves was evident (grades III and IV).

With the exception of a small number of cases in which the patients complained of vague joint pains or mild chorea continuing over a period of months or, in some cases, years, repeated attacks of polyarthritis were separated by quiescent periods free from symptoms, and the cases could be divided into groups depending on the number of these attacks. The group of cases in which joint pains had been noticeable over a period of years or in which chorea had been continuous are designated as continuous. The following tabulation shows the relation between the number of attacks of symptoms and the severity of valvular damage:

No. of Attacks	Total No. of Cases	Grade of Deformity, No. of Cases				Deformity of Grade I or II Percentage of Cases	Deformity of Grade III or IV, Percentage of Cases
		I	II	III	IV		
1	57	10	16	17	14	45	55
2	20	4	5	7	4	45	55
3 to 7	11	1	5	3	2	55	45
Continuous	10	0	2	4	4	20	80

There is no significant correlation between the number of attacks and the degree of valvular deformity except in the small group of cases in which symptoms were "continuous."

The following tabulation shows the frequency of different grades of valvular lesions when the cases are divided according to the length of the interval between the onset of symptoms and the time of death:

Interval Between Onset of Symptoms and Death, Yr.	Total No. of Cases	Grade of Deformity, No. of Cases				Deformity of Grade I or II, Percentage of Cases	Deformity of Grade III or IV, Percentage of Cases
		I	II	III	IV		
0-4	14	8	4	2	0	85	15
5-9	14	2	9	3	0	78	22
10-19	27	1	6	10	10	24	76
20-29	21	2	4	6	9	28	72
30 +	22	2	3	11	6	22	78

It is noteworthy that when less than ten years has elapsed between onset and death, the valves are usually not stenosed (grades I and II) and the most advanced lesions (grade IV) do not occur. After ten years, however, the incidence of stenotic valves is much increased.

The following tabulation shows that the duration of the disease is more significant in determining the degree of valvular deformity than the number of attacks or the age at which onset occurs:

	Grade of Valvular Deformity			
	I	II	III	IV
Mean number of attacks.....	1.60	1.72	1.74	1.40
Mean age at onset, yr.....	17.2	13.6	15.1	14.1
Mean age at death, yr.....	27.3	28.8	39.3	37.8
Mean duration of disease, yr.....	11.1	15.2	24.2	23.7

#### COMMENT

Though exact definition of the relation between the Aschoff body and the clinical picture of rheumatic fever is not possible at this time, there is evident correlation between age, symptoms and Aschoff bodies. Although polyarthritis preceding death by less than five months was found at autopsy to be invariably accompanied by Aschoff bodies, these lesions were not always preceded by manifest polyarthritis, and in a few cases the existence of rheumatic infection was first ascertained on autopsy.

The course of rheumatic heart disease has two fairly distinct stages, approximately separated by the third decade of life. Cardiac failure is associated in the first stage with the presence of Aschoff bodies in the myocardium and in the second with advanced valvular deformity. In the first three decades of life symptoms of rheumatic fever and Aschoff

bodies are relatively common and are accompanied by minimal valvular deformity. Under such circumstances cardiac failure must be attributed to the myocardial involvement, since cardiac failure with minor degrees of deformity and absence of Aschoff bodies occurs only rarely. In the later decades, when cardiac failure can be attributed to advanced valvular deformity, Aschoff bodies are seldom found and have scant, if any, part in the production of cardiac failure.

Rothschild, Kugel and Gross<sup>5</sup> attributed cardiac failure in the first five decades of life to injury of the myocardium, as shown by the presence of Aschoff bodies, rather than to a mechanical defect produced by a valvular lesion. Swift and McEwen<sup>6</sup> stated that cardiac failure does not occur in young persons with rheumatic fever, even when valves are deformed, unless there is accompanying disease of the myocardium. The observations described here confirm these statements in their application to young persons but indicate that cardiac failure in later life is the result of valvular lesions.

Since the degree of valvular deformity appears to determine the appearance of cardiac failure in the later decades, the factors which influence the degree of deformity are important. Wilson<sup>7</sup> asserted that there is apparently a direct relation between the degree of cardiac damage and the number and severity of recurrences. Injury to the heart, she stated, is frequently insidious and subclinical, progressing with time even in the absence of manifestations of active infection. In the cases that are discussed here it is noteworthy that the only factor that has been found to increase the severity of valvular deformity is the duration of the disease.

#### SUMMARY

Of 98 cases in which endocarditis or pericarditis, found at autopsy, had been preceded by a history of rheumatic fever with polyarthritis or other similar manifestations of disease, Aschoff bodies were found in all in which death occurred during the first decade of life, in 64 per cent of those in which it occurred during the second decade and in 11 per cent of those in which it occurred during a later decade.

When Aschoff bodies were found in the myocardium (28 cases) with 1 exception the interval between the last attack of polyarthritis and death was five months or less.

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5. Rothschild, M. A.; Kugel, M. A., and Gross, L.: The Incidence and Significance of Active Infection in Cases of Rheumatic Cardiovascular Disease in the Various Age Periods, *Am. Heart J.* 9:586, 1934.

6. Swift, H. F., and McEwen, C.: Rheumatic Fever, in Christian, H. A.: *Oxford Medicine*, New York, Oxford University Press, 1938, vol. 5, pt. 1, pp. 11-38.

7. Wilson, M. G.: *Rheumatic Fever*, New York, Commonwealth Fund, Division of Publications, 1940.

In 3 cases in which Aschoff bodies occurred in the myocardium there was no history of polyarthritis, chorea or other clinical evidence of acute rheumatic infection.

A curve of the frequency of death in cases in which the symptoms of rheumatic fever and cardiac lesions occurred at different age periods shows two distinct peaks, one in the first decades of life, corresponding with deaths from cardiac failure and the presence of Aschoff bodies in the myocardium, and the other between the ages of 40 and 60 years, associated with cardiac failure, deforming lesions of the valves and an absence of Aschoff bodies.

Minor degrees of valvular deformity preponderated in the first three decades of life, whereas advanced deformity was common in the later decades. Valvular deformity increased with the duration of the disease after the onset of symptoms but had no constant relation to the number of attacks or to the age at onset.

# PULMONOCARDIAC FAILURE AS A RESULT OF SPINAL DEFORMITY

## REPORT OF FIVE CASES

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An extreme deformity of the spine is generally acknowledged to be a handicap both in the physical and in the social life of the person afflicted. That the resulting distortion of the thoracic organs may have fatal consequences has not been widely recognized in the English-speaking world. For many years continental writers, even in textbooks, have described this syndrome, which has been termed "pulmonocardiac failure."

Chapman, Dill and Graybiel,<sup>1</sup> of the Harvard Fatigue Laboratory, recently reviewed the subject of pulmonocardiac failure and were able to find 126 fatal cases recorded in the literature. They reported the clinical and laboratory data in 12 cases of their own, in 4 of which the patients died. In their investigation they paid particular attention to the ill effects on respiratory function.

My interest in this subject was aroused by encountering 2 instances of this condition within a period of two months during the course of routine autopsies. Search of the files in this department back as far as the beginning of 1925 revealed 3 other instances among 6,700 autopsies. An analysis of the clinical and postmortem observations in these 5 cases form the basis for this report.

## REPORT OF CASES

CASE 1.—H. C., a 75 year old man, was admitted to the Toronto General Hospital, service of Prof. Duncan Graham, on Oct. 19, 1933. He gave a history of slight dyspnea on exertion during the previous year but had been able to carry on his usual job as a cleaner in a laundry without real difficulty. Three weeks before admission he noticed an unusual degree of shortness of breath after climbing a flight of stairs. A week later, while working, he suddenly became short of breath and weak and had to rest frequently. In the evening of the same day his feet began to swell, but the swelling had disappeared by the following morning

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From the Department of Pathology, University of Toronto, and Toronto General Hospital.

1. Chapman, E. M.; Dill, D. B., and Graybiel, A.: The Decrease in Functional Capacity of the Lungs and Heart Resulting from Deformities of the Chest: Pulmonocardiac Failure, *Medicine* 18:167 (May) 1939.

and did not recur. He was forced to give up work, as the slightest exertion caused him severe respiratory distress. He was confined to his room but did not go to bed prior to admission.

On examination the patient was very dyspneic and showed marked cyanosis of the face. There was a severe deformity of the chest due to an extreme left-sided scoliosis involving most of the thoracic portion of the spine. He stated that he had had this deformity as long as he could remember, and no history of its onset or progress could be obtained. The heart was thought to be normal in size, and there were no murmurs. The blood pressure was 120 systolic and 80 diastolic, and the pulse was regular, with a rate of 74 per minute. Respirations were 30 per minute. Numerous rales were heard at the bases of both lungs. The edge of the liver was palpable 3 fingerbreadths below the costal margin. No pitting edema was present. There were no other significant physical findings.

Routine examination of the blood and urine revealed no important abnormalities. An electrocardiogram showed a voltage of 5 mm. with negative T waves in leads II and III and a tendency to right axis deviation.

The clinical diagnoses were chronic degenerative myocarditis and cardiac insufficiency with kyphosis of the spine. Because of the fairly rapid onset of symptoms and the abnormal T waves, cardiac infarction was also considered to be a possibility.

The patient was put to bed, and the diet was restricted in fluids and salt. A subsequent electrocardiogram showed a positive T wave in lead II, a change which was regarded as supporting the diagnosis of cardiac infarction. He continued to be dyspneic, the respirations varying between 20 and 38 per minute; the cyanosis deepened. The pulse rate never rose above 98 per minute; terminally the blood pressure fell to 98 systolic and 70 diastolic. Death occurred suddenly during the early morning of October 23, four days after admission.

*Autopsy.*—The body measured 150 cm. in length and weighed 135 pounds (61.2 Kg.). The face and fingers were extremely cyanosed; there was no edema of the legs. The chest was short and barrel shaped because of the spinal deformity, which consisted of a sharp, extreme curve to the left starting at the first thoracic vertebra and passing out nearly to the left axilla, the apex being formed by the seventh thoracic vertebra. From here the vertebral column passed downward and medially in an S-shaped curve to the sacrum. The cut surface of the lumbar portion of the spine was unusually soft and porous in consistency and pink in color; in the thoracic portion it was somewhat firmer in texture and had a grayish tinge. No evidence of tuberculosis was seen.

The pericardial sac contained 60 cc. of clear fluid. The heart weighed 410 Gm. The right auricle and ventricle were greatly dilated and filled with clot. The myocardium of the right ventricle measured 8 mm. in thickness and that of the left 15 mm.; no scarring was present on the cut surface. A slight degree of sclerosis of the coronary arteries was evident but much less than one might reasonably expect in so old a man; there was no stenosis of the arteries anywhere. No valvular lesions were seen, and there was no dilatation of the valve orifices. The aorta followed the course of the spine throughout and was not constricted at any point. The lungs were small, each weighing 265 Gm. They were crepitant throughout. The branches of the pulmonary artery were not dilated; many yellowish atheromatous nodules were scattered along the intima. No other lesions were noted in the lungs. Each pleural cavity contained 150 cc. of transudate. Two



hundred cubic centimeters of clear fluid was also present in the peritoneal cavity. The liver was small, weighing 1,120 Gm.; the cut surface showed the characteristics of passive congestion. There were no other gross findings of importance.

*Microscopic Examination.*—The sections of heart stained by hematoxylin and eosin were normal, but in those stained with sudan IV many fine fat droplets were seen dotting the muscle fibers. In the lungs there was congestion of the capillaries and a few of the alveoli contained edema fluid. Some of the alveoli were partially collapsed; the walls appeared to be of normal thickness. No significant sclerosis was noted in the small arteries or arterioles. Well developed chronic passive congestion was evident in the liver. In the thoracic vertebrae the trabeculae were scanty and rather thin but otherwise not remarkable. The marrow did not contain any lesions. None of the other organs sectioned revealed any significant abnormalities.

*Diagnosis.*—The principal anatomic diagnoses were osteoporosis of the spine (cause undetermined), scoliosis of the thoracic and lumbar portions of the spine, hypertrophy and dilatation of the right auricle and ventricle, fatty degeneration of the heart, atherosclerosis of the pulmonary artery, hydrothorax, ascites and passive congestion of the liver.

CASE 2.—A. F., a 58 year old man, was admitted to the medical service of the Toronto General Hospital on April 16, 1935. He had always been more or less short of breath on exertion, a disability which he himself attributed to his thoracic deformity. About four months before admission his landlady had drawn his attention to the bluish color of his face and neck, which was present intermittently and was more noticeable after exercise. For the past two months there had been a definite increase both in the dyspnea and in the cyanosis. Two weeks before admission he began to have swelling of the feet and legs toward evening; this usually had disappeared by the following morning. There was no precordial pain, palpitation or cough. An extreme curvature of the spine had been present ever since birth.

On examination the patient showed severe cyanosis of the face and neck but did not appear to be in acute respiratory distress. The eyelids were slightly swollen and the scleral vessels were congested. The chest was short, narrow and deep, because of marked left-sided scoliosis of the thoracic portion of the spine with slight lordosis in the lower part. The size of the heart could not be estimated clinically; there were no murmurs. The pulse was regular, the rate being 96 per minute. The blood pressure was 120 systolic and 66 diastolic. Many moist rales were heard throughout both sides of the chest. In the right side of the chest posteriorly there was one small patch of bronchial breathing. The liver was not enlarged. Pitting edema was detected up to the level of the knees.

Routine laboratory examination failed to reveal any abnormality of urine or blood. The Wassermann reaction of the blood was negative. An electrocardiogram showed a voltage of 8 mm. and right axis deviation; the T wave in lead II was flat, and the T wave in lead III was negative. On fluoroscopic examination the heart was thought to be enlarged, but the thoracic deformity made any definite conclusion impossible. Patchy consolidation was observed throughout both lungs and was thought to be pneumonic in character.

A diagnosis of chronic degenerative myocarditis with cardiac failure and bronchopneumonia was made; because of the extreme cyanosis of the face, the presence of tumor or aneurysm in the superior part of the mediastinum was suspected.

The patient's temperature varied between 99 and 101.4 F. and his pulse between 90 and 110 per minute, never being over 120 per minute. On one occasion it was observed that the blood pressure in the right arm was 118 systolic and 78 diastolic and that in the left arm was 96 systolic and 64 diastolic. His course was progressively downhill, and he died on April 23, after one week in the hospital.

*Autopsy.*—The body was that of a small man with a short neck and the head sunken between the shoulders. It weighed 125 pounds (56.7 Kg.) and measured 140 cm. in length. The face and neck were deeply cyanosed, the lips being almost black. The veins of the neck were greatly distended. The eyes were bulging, the eyelids edematous and the conjunctivas much congested. Pitting edema was evident up to the midthigh level. Extreme left-sided scoliosis was present in the midthoracic region, with bulging of the left side of the chest and narrowing of the sternum anteriorly. Except for the distortion of the vertebrae, the cut surface of the spine showed no lesions.

The heart was rather large and globular and weighed 375 Gm. The pericardial sac contained 100 cc. of clear fluid. Much dark red, fluid blood welled up from the severed ends of the pulmonary vessels; the superior vena cava was distended. The right ventricle was dilated and greatly hypertrophied, its wall measuring 14 mm. in thickness, the same as that of the left ventricle. No valvular lesions were seen. The orifice of the tricuspid valve measured 11 cm. in circumference and that of the pulmonary valve 7.3 cm. The right auricular appendage was filled with a thrombus. Slicing of the myocardium failed to reveal any lesions. The coronary vessels contained many atheromatous plaques but were widely patent except at one point 2 cm. from the origin of the anterior descending branch, where the lumen was almost occluded. The aorta was small, measuring 4.5 cm. in its greatest circumference; it was closely applied to the spine in the latter's tortuous course but was not obstructed.

The right pleural cavity was occupied by 100 cc. of yellow transudate; the left was empty. The lungs were both small, the left weighing 350 Gm. and the right 310 Gm. Because of the thoracic deformity the left lung lay in an almost horizontal position. Both lungs were congested, and poorly defined areas of consolidation could be felt in the upper lobe of the left lung and the lower lobe of the right one. Elsewhere the cut surface was flabby, dark red and moist. No stenosis of the pulmonary arteries was evident, but examination of the intimal surface disclosed numerous discrete yellowish atheromatous plaques.

Six hundred cubic centimeters of ascitic fluid was removed from the peritoneal cavity; the intestine was everywhere edematous; the hemorrhoidal veins were distended and filled with thrombi. The liver weighed only 900 Gm. and was deeply congested. The rest of the abdominal organs were not remarkable except for congestion.

*Microscopic Examination.*—Sections of the heart muscle did not reveal any fibrosis or other lesion. In the lungs there was much congestion and many of the alveoli were partially collapsed; hemorrhage had occurred into the air spaces, which also contained macrophages laden with blood pigment. There was no thickening of alveolar walls. Some of the small branches of the pulmonary artery contained patches of intimal hyaline thickening in their walls, but there was no significant narrowing of the lumens; the arterioles appeared normal. No inflammatory changes were observed. In the liver a severe degree of chronic passive congestion was evident. The sinusoids of the central and midzonal portions of the lobules were distended with red cells, the liver cords being much compressed. No important lesions were encountered in the other organs.

*Diagnosis.*—The chief anatomic diagnoses were scoliosis and lordosis of the thoracic portion of the spine (congenital), hypertrophy and dilatation of the right ventricle (extreme), atherosclerosis of the pulmonary artery, passive congestion of the lungs and liver, hydrothorax (left side), hydropericardium, ascites and edema of the legs.

CASE 3.—R. L., a 49 year old man, was admitted to the medical service of the Toronto General Hospital on June 20, 1936. He was so ill that a detailed history could not be obtained. Ten years previously he had been told that he had heart disease, but he apparently had had no symptoms until three months before admission, when he began to have dyspnea, which grew progressively worse. One week before admission this became so severe that he had to remain in bed in a prone position with his head propped on his hands.

Examination revealed a hunchback in acute respiratory distress. Cyanosis was marked and breathing was labored and rapid, the respiratory rate being 60 per minute. Extreme kyphosis was present in the midthoracic portion of the spine. A history was later obtained from the brother that the patient had suffered an injury of his spine at the age of 2 years and the deformity had dated from that time. The size of the heart could not be determined; the heart sounds were faint and no murmurs were heard. The apex rate was 150 per minute and the beat was regular. The blood pressure could not be accurately determined, but the systolic pressure was less than 40 mm. of mercury. Moist rales were heard at the bases of both lungs. The edge of the liver was palpable 4 fingerbreadths below the costal margin. Pitting edema was absent.

A diagnosis of chronic degenerative myocarditis with cardiac failure was made.

One half milligram of a glucoside from *Digitalis lanata* (digoxin) was given intravenously, and in half an hour the pulse rate had decreased to 120 per minute; respiration dropped to 30 per minute, and the cyanosis deepened. The patient's condition became progressively worse, and in spite of the administration of caffeine and coramine (a 25 per cent solution of pyridine betacarboxylic acid diethylamide) he died two hours after admission.

*Autopsy.*—The body was that of a poorly nourished, hunchbacked man, measuring 144 cm. in length and weighing 85 pounds (38.6 Kg.). Cyanosis of the face, ears and buccal mucosa was prominent. Extreme kyphosis of the midthoracic portion of the spine was present, accompanied by marked pigeon breast deformity. The cut surface of the spine was normal in appearance. No dependent edema was demonstrated. The pericardial fluid amounted to only 15 cc. The heart lay farther to the left of the midline than usual, and almost the whole of its anterior surface was formed by the right ventricle, which was greatly dilated and hypertrophied; its wall was 10 mm. in thickness, while that of the left ventricle was 14 mm. The heart weighed 360 Gm. No valvular lesions were evident; the tricuspid valve measured 11.5 cm. in circumference and the pulmonary valve 7.5 cm. The coronary arteries were dotted with numerous atherosclerotic plaques, but there was no significant stenosis. The cut surface of the interventricular septum was flecked by a few small patches of fibrosis. The aorta was acutely angulated at its arch, but no important degree of obstruction was obvious.

The right pleural cavity did not contain fluid, but there was 75 cc. of clear amber fluid in the left one. The left lung weighed 327 Gm. and the right 310 Gm. Both were congested and rather moist. The intima of the pulmonary arteries was occupied by many atheromatous patches. No fluid was found in the peritoneal sac.

The liver weighed 923 Gm. and presented no abnormalities. The other organs were not remarkable except for an adenoma beneath the capsule of the right kidney and a benign ulcer on the lesser curvature of the stomach near the pylorus.

*Microscopic Examination.*—In the heart a few small patches of fibrosis were evident. Several of the branches of the coronary arteries showed some medial hypertrophy. Sections of the lungs revealed partial collapse of alveoli, with slight fibrous thickening of their walls and patchy congestion. A few collections of heart failure cells were seen. In the small branches of the pulmonary artery hyaline intimal plaques were visible, but these had no significant effect on the size of the lumens. The arterioles, however, had a greatly hypertrophied media, such that the lumens were on the average reduced in size by a third. The liver presented slight passive congestion around central vein areas.

CASE 4.—P. M., a 31 year old man, was admitted to the Toronto General Hospital, service of Prof. Duncan Graham, on Oct. 29, 1940. For the past ten years he had been rather tired and somewhat short of breath on exertion but not sufficiently so that the condition interfered with his work. About five months before admission he noticed a definite increase in his fatigue and an intermittent dry cough developed. One week before admission he had a "chill," followed by fever and generalized aches. During the rest of this week he had some difficulty in getting his breath and experienced increased cough, with scanty white sputum and frequent attacks of nausea and vomiting. His physician found many rales and rhonchi in his chest and sent him to the hospital with the diagnosis of "flu."

On admission the patient was rather drowsy, slightly cyanosed and dyspneic. He complained of dimness of vision, apparently of recent onset. There was well marked kyphosis of the thoracic portion of the spine with some scoliosis to the left. At the age of 5 he had had tuberculosis of the spine, resulting in this deformity, which had apparently not progressed in recent years. Examination of his eyes revealed that he could only distinguish light from dark, but no basis for this could be found. Many rhonchi and rales were heard throughout the chest. The heart seemed to be enlarged to percussion; there were no murmurs. The pulse was regular, the rate being 80 per minute. The blood pressure measured 170 systolic and 90 diastolic. The liver was not palpable, and there was no dependent edema. Neurologic examination showed exaggeration of all tendon reflexes and an exhaustible ankle clonus.

Laboratory examination revealed that the urine had a specific gravity of 1.010, with a 1 plus reaction for albumin and a few white blood cells. The Wassermann reaction of the blood was negative, and the nonprotein nitrogen content of the blood was 172 mg. per hundred cubic centimeters.

A diagnosis of hypertensive heart disease, pulmonary edema and uremia was made.

The next day the patient was more drowsy, and intermittent twitching of the left leg developed, which was followed two hours later by clonic spasm of all limbs and conjugate deviation of the eyes to the right; this attack lasted about two minutes. During this time he did not lose consciousness but became more deeply cyanosed than usual. It was noted that the cyanosis was especially marked over the head, neck and upper part of the chest; there was also much engorgement of the veins of the neck and arms. These findings rather suggested a mediastinal tumor, but roentgenologic examination of the chest did not confirm this diagnosis. Convulsions continued at irregular intervals for the next two days. An electrocardiogram showed a voltage of 7 mm. and depressed RT segments in

leads II and III. Treatment consisted of the administration of sedatives, intravenous injection of dextrose solution and use of an oxygen tent; on one occasion a venesection was performed, 400 cc. of blood being removed. The venous pressure in the left arm was 360 to 380 mm. of water and in the left leg 290 mm. On October 31 the pulse was regular, with a rate of 100 per minute, and the blood pressure was 150 systolic and 110 diastolic. The nonprotein nitrogen content of the blood had fallen to 146 mg. per hundred cubic centimeters, and the creatinine content was 6 mg. per hundred cubic centimeters. The urine contained a tract of albumin and an occasional white blood cell. On November 1 the patient became semiconscious; the level of nonprotein nitrogen rose to 154 mg. per hundred cubic centimeters and the level of creatinine to 9.4 mg. During the night of November 2 he had another convulsion, became comatose and died, four days after admission.

*Autopsy.*—The body measured 140 cm. in length and weighed 103 pounds (46.7 Kg.). A severe degree of kyphosis with slight scoliosis to the left side was noted in the upper and middle thoracic regions. Externally the vertebral bodies appeared normal except for their deformity. Only the lower thoracic and the lumbar portion of the spine were removed, and their cut surfaces revealed no lesions; the marrow was deep red. Cyanosis was present over the face and neck. No dependent edema was detected. The pericardial sac contained a normal amount of fluid.

The heart showed considerable dilatation of the right auricle and ventricle and weighed 250 Gm. The valves were normal and the valve rings were not enlarged. The coronary arteries were widely patent, thin walled and smooth. The right ventricular wall was somewhat hypertrophied, measuring 7 mm. in thickness, while the left measured 12 mm. The cut surface of the myocardium presented a normal appearance. The aorta followed closely the curve of the spine but aside from this distortion was not remarkable.

The left pleural cavity was much smaller than the right one, but the antero-posterior diameter of each was much increased. No fluid was found in the pleural sacs. The left lung was small and partially collapsed, weighing 280 Gm.; the right was of normal size and weighed 510 Gm. The whole of the left lung, as well as the upper lobe of the right lung, showed congestion. The cut surfaces were moist and dull red. The intima of the pulmonary arteries was normally smooth and glistening throughout. The peritoneal cavity did not contain any fluid.

The liver weighed 1,490 Gm. and the cut surface was congested. The kidneys were congested but otherwise normal.

*Microscopic Examination.*—No abnormality was found in the heart. Section of the left lung revealed some collapse; there was much congestion of the capillaries, and many of the alveoli were filled with red cells and edema fluid; numerous macrophages filled with blood pigment lay free in the alveolar spaces. No thickening of the alveolar walls was evident. Essentially the same picture was present in the upper lobe of the right lung and to a much less degree in the lower lobe; here a few patches of emphysema were noted. In no section did the pulmonary vessels present any abnormality. The central vein areas of the liver were occupied by collapsed stroma, in the meshes of which were caught red blood cells and globules of bile pigment. There was much destruction of the parenchymal cells in the central zones. These changes were fairly well localized to the central zone, but the remainder of the lobule also showed widening of the sinusoids. The kidneys showed only congestion. No other important lesions were noted in any organ.

*Diagnosis.*—The anatomic diagnosis included kyphosis and scoliosis of the thoracic portion of the spine (tuberculous?), hypertrophy and dilatation of the right auricle and ventricle and passive congestion of the lungs, liver and kidneys. No significant lesions were present in the kidneys, and the elevation of the non-protein nitrogen and the creatinine content of the blood could not be explained on a renal basis.

CASE 5.—F. D., a 53 year old man, was admitted to the medical service of the Toronto General Hospital on Dec. 14, 1940. He gave a history of having caught a head cold two weeks before; he felt well till two days before admission, when fatigue, malaise, anorexia and dry cough developed and forced him to go to bed. The day before entering the hospital he was short of breath even at rest and felt feverish. On close questioning he reluctantly admitted that he had been getting increasingly short of breath for some years and more especially in the past four months; his ankles had recently begun to swell toward evening but were normal by morning. For six weeks he had had frequent attacks of nocturnal dyspnea, usually about 6 a. m. He also stated that his mother had died of pulmonary tuberculosis when he was 1 year old and that shortly after tuberculosis of the spine had developed.

On examination he was dyspneic and had a grayish cyanosis. There was extreme kyphosis of the dorsal portion of the spine with pectus carinatum. The only abnormalities in the lungs were diminished breath sounds at the base of the left lung and rales at the base of both lungs. The size of the heart could not be estimated. There were no murmurs. The pulse was regular, with a rate of 98 per minute; the blood pressure measured 130 systolic and 60 diastolic. The edge of the liver was palpable 3 fingerbreadths below the costal margin. Dependent edema was not present. The rectal temperature was 101 F.

Laboratory examination of the blood and urine revealed nothing significant. The Wassermann reaction of the blood was negative and the nonprotein nitrogen content was 50 mg. per hundred cubic centimeters.

Having case 4 in mind, the clinician made a diagnosis of pulmonocardiac failure, with possible bronchopneumonia.

The patient was placed in an oxygen tent and given theophylline with ethylene diamine; he showed some temporary improvement, though dyspnea and cyanosis remained. On December 30 he became much worse; cyanosis and dyspnea were extreme, and the pulse rate rose to 160 per minute. In spite of intravenous administration of digifoline and venesection, he died on December 31, after seventeen days in the hospital.

*Autopsy.*—The body was that of a moderately well nourished, hunchbacked man, measuring 148 cm. in length and weighing 97 pounds (44 Kg.). Extreme kyphosis was present in the lower thoracic region, the apex of the knuckling forming an angle of about 30 degrees. Anteriorly there was a well developed pigeon breast deformity of the sternum, its apex being a handbreadth above the level of the lower sternal border. Dependent edema was present only in the scrotum.

The pericardial sac contained no excess fluid. The heart weighed 375 Gm., and its chambers were not notably dilated. The valve cusps were normal and the orifices were not enlarged, the orifice of the tricuspid valve measuring 12.5 cm. in circumference and that of the pulmonary valve 9 cm. The left anterior descending coronary artery showed severe sclerosis, with calcification and stenosis throughout most of its length; the involvement of the other branches was minimal. The wall of the left ventricle measured 15 mm. in thickness and that of the right 5 mm.

The cut surface of the myocardium presented no abnormalities. The aorta followed the course of the spine and was sharply kinked just above the celiac axis, in the hollow of the kyphotic portion of the spine. A thick, firm ridge projected inward from its anterolateral surface, narrowing the lumen by about a third.

The thoracic cage was small and deformed. The left pleural sac contained a few cubic centimeters of amber fluid; the right one was empty. Both lungs were small, the left weighing 245 Gm. and the right 295 Gm. The posterior portion of each lung was somewhat bluish, doughy and collapsed; elsewhere both lungs were normally crepitant. Opening the branches of the pulmonary artery disclosed a moderate number of yellowish patches in the intima. The liver was somewhat square and weighed 1,400 Gm. No lesions were obvious on the cut surface.

Sagittal section of the spine showed the angulation to be about 4 cm. above the end of the spinal cord. It was not possible to identify the various vertebrae, since the disks had almost completely disappeared from the seventh thoracic to the fifth lumbar vertebra, which section of the spine measured only 9 cm. in total length. At the point of angulation the vertebral bodies and the spinous processes were involved in an old fibrocaseous tuberculous process. The spinal cord was not compressed.

*Microscopic Examination.*—Sections of heart muscle from the lateral walls of both ventricles and the septum revealed only questionable medial hypertrophy of some of the arterioles. In the lungs there was moderate congestion of the capillaries and many alveolar spaces were filled with edema fluid and a sprinkling of macrophages, some filled with brown pigment. Patchy areas of collapse alternated with areas of emphysema. There was no thickening of the alveolar walls. In only one area did the pulmonary arteries present any abnormality. Here they showed well developed endarteritis in an area of scarring infiltrated with lymphocytes, the appearance being suggestive of a healed tuberculous lesion. The veins were normal. In the liver there was some dilatation of the central portions of the sinusoids. Sections of the vertebrae revealed zones of caseous necrosis, with dead bone alternating with areas of new bone formation.

#### ANALYSIS OF CASES

Pulmonocardiac failure as a result of severe deformity of the spine is not often seen in routine autopsies. In this series it was present on an average of only once in every 1,340 cases, or in approximately 0.075 per cent. It has been pointed out, however, that the condition is of frequent occurrence in persons so deformed. This is confirmed in our autopsy records by the discovery of only 1 case, not reported here, in which the patient suffered from extreme deformity of the vertebrae and died of intercurrent disease.

*Clinical Observations.*—It has been emphasized that persons with such deformity tend to die in early adult life, the average age at death having been given as 30 years. In this small series that poor prognosis was not borne out, the average age at death being 53 years. Only 1 patient was sufficiently young to be noteworthy. The claim of Dedic<sup>2</sup> that patients thus deformed rarely pass the age of 40 was not substantiated.

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2. Dedic, S.: La cardiopathie cyphotique, Arch. d. mal. du cœur **23**:33, 1930.

Spinal deformities from whatever cause are known to be more common in men than in women, as is also pulmonocardiac failure. In all of these cases the patients were men.

A combination of kyphosis with well marked scoliosis is usually seen, but in 2 instances of deformity in this series, 1 due to injury and in the other to tuberculosis, kyphosis alone was present: in 1 other the kyphosis was predominant, the scoliosis being of minimal degree. In both the cases in which scoliosis was the main deformity the primary curve was to the left, as it was also in the case of kyphoscoliotic curvature. This finding is contrary to the usual experience, in which right-sided scoliosis is by far the commoner.

Symptoms, sometimes of only mild degree, were usually present for several years, or even as far back as the patient could remember. However, the length of time from the onset of the more acute manifestations to death was relatively short, only several months, and rapid deterioration of the patient's condition usually took place in the last few days. Dyspnea was the major symptom in all cases. It was often present for some years, but the patient was able to carry on with little trouble until a relatively sudden exacerbation marked the onset of the final illness. One patient could obtain relief only by lying prone with his head propped on his hands. Nocturnal dyspnea was mentioned in 1 case. Four of the patients had a history of recent, intermittent swelling of the feet, but in only 1 was this symptom present on admission. Palpitation and precordial pain were not complained of in this series. The sudden fainting attacks mentioned by various authors did not occur.

Cyanosis was evident in all cases, and involved chiefly the head and neck; in 1 case this was first noticed by another person. In 2 cases this fairly localized distribution of the cyanosis, together with dilatation of the veins, suggested a mass in the superior portion of the mediastinum. Respirations were usually labored, and the rate increased to the neighborhood of 30 per minute; terminally this rate was doubled in 2 cases.

The size of the heart was difficult to determine clinically owing to the thoracic deformity, and in most cases an opinion on this point was not even expressed. Teleroentgenograms were not made. No murmurs were detected in any case. In no case was any mention of accentuation of the pulmonic second sound made; it is possible that this would have been noted if it had specifically been looked for. The pulse rate was somewhat increased but was rarely over 120 per minute except just before death. No abnormalities of rhythm were detected. In only 1 case was the blood pressure elevated, and in this case the patient probably was suffering from essential hypertension not connected causally with the pulmonocardiac failure.

In the 3 cases in which electrocardiograms were made the voltage tended to be low, varying from 5 to 8 mm. In case 1 there was a



tendency to right axis deviation with negative T waves in leads II and III, those in the latter being cove plane in type. The T wave in lead II became positive three days later, then reverted to negative the following day. This was thought to be indicative of cardiac infarction, but the diagnosis was not confirmed at autopsy. These changes are probably more suggestive of relatively acute right ventricular strain (Barnes<sup>3</sup>); it will be remembered that in this case the onset of acute symptoms occurred less than a month before death. However, the thickness of the wall of the right ventricle is evidence of chronic right ventricular strain as well. In case 2 there was right axis deviation, the T wave in lead II was flat and the T wave in lead III was negative. These changes are regarded as among those characteristic of right

*Pathologic Data in Five Cases of Pulmonocardiac Failure Resulting from Spinal Deformity*

Case No.	Age, Yr.	Sex	Spinal Deformity	Cause of Spinal Lesion	Weight of Heart, Gm.	Dilatation of Heart	Thick-ness of Wall of Right Ventricle, Mm.	Com-bined Weight of Lungs, Gm.	Pulmo-nary Athero-scle-rosis
1	75	♂	Scoliosis (left)	Osteo-porosis	410	Right auricle and ventricle	8	530	+++
2	58	♂	Scoliosis (left) with slight lordosis	Congen-ital	375	Right ventricle	14	660	+++
3	49	♂	Kyphosis	Injury	360	Right ventricle	10	637	+++
4	31	♂	Kyphosis with slight scoliosis (left)	Tubercu-losis (?)	250	Right auricle and ventricle	7	790	0
5	53	♂	Kyphosis	Tubercu-losis	375	None	5	540	++

ventricular strain.<sup>3</sup> It is noteworthy that this was the case in which the wall of the right ventricle measured 14 mm. in thickness. In case 4 there was only slight depression of the RT segments in leads II and III.

The only signs of congestive failure consistently present were rales at the bases of the lungs. As noted in the preceding section, edema of the legs was demonstrated in only 1 case. In 3 cases the lower edge of the liver was palpable well below the costal margin. Since the livers at autopsy were all small with the exception of 1, which weighed 1,490 Gm. but was not palpable clinically, it seems likely that this was due to the decreased capacity of the thorax and the low position of the diaphragm.

*Postmortem Observations (Table).*—In this series the weights of the hearts ranged from 250 to 410 Gm. In normally developed people

3. Barnes, A. R.: *Electrocardiographic Patterns*, Springfield, Ill., Charles C. Thomas, Publisher, 1940.

the heart weight is best correlated with the body weight. No "normal" figures of heart weights have been published for the deformed persons represented in this series. There are obvious fallacies in applying figures for normal persons to these patients in the determination of cardiac hypertrophy. Comparison of the figures reported here, however, with those established by Smith<sup>4</sup> as normal gives one the definite impression that hypertrophy was present in at least 4 cases. More reliable evidence of hypertrophy is furnished by measurement of the thickness of the right ventricular wall. In 4 cases the hypertrophy was well marked, the thickness of the right ventricle varying from 7 to 14 mm.; in case 2 its measurement equaled that of the left ventricle. In only case 5 could there be any doubt about the right ventricular hypertrophy, since the wall was but 5 mm. thick. Dilatation of the right side of the heart was present in 4 cases. In 2 cases only the ventricle was involved, and in the other 2, both auricle and ventricle suffered. No dilatation could be found in case 5. Hypertrophy of the left ventricle was not seen in any case. Valvular lesions were not observed in any case, nor was any enlargement of the orifices of the tricuspid and pulmonary valves detected. Arteriosclerosis of the coronary arteries in the cases of the 4 older patients was not unusually severe; in 2 cases only was stenosis of a coronary artery present, in both cases in the anterior descending branch. In only 1 case was any gross lesion apparent on section of the myocardium, and that was only a few small patches of fibrosis.

In each case the aorta closely followed the course of the spine, but no significant degree of obstruction was demonstrated.

Small amounts of transudate were frequently present in the pericardial, pleural and peritoneal cavities.

In all patients the lungs were small; the combined weight of the two lungs varied from 530 to 790 Gm. Several factors affect the evaluation of these figures. Congestion and edema, which increase the weight, were present in all. On the other hand, the fact that these persons were underdeveloped must be taken into account in estimating what would be normal for them. In cases 4 and 5, in which the patients were observed personally, one had the definite impression that there was less than the normal amount of lung tissue present. Atherosclerosis was moderate to severe in the larger branches of the pulmonary artery in 4 of the 5 cases. In case 4 no intimal changes were seen. Pulmonary infection was not a factor in any case.

Significant microscopic abnormalities were strikingly lacking. One heart showed fatty degeneration; another had a few areas of fibrosis, and the rest appeared normal. In the lungs no important changes were

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4. Smith, H. L.: The Relation of the Weight of the Heart to the Weight of the Body and of the Weight of the Heart to Age, *Am. Heart J.* 4:79, 1928.

evident. Collapse, congestion, edema and heart failure cells were noted. The alveolar walls were not thickened. In 4 cases the small pulmonary vessels were normal; in case 5 there was considerable medial hypertrophy of the arterioles.

Congestion of the liver and other organs were the only other relevant findings.

#### COMMENT

The general clinical pattern in this series of 5 cases was similar to that already described in the literature. Most of these patients survived a longer period than usual, but once acute symptoms developed the disease rapidly progressed to a fatal outcome.

The only fairly constant pathologic findings were hypertrophy and dilatation of the right side of the heart, atherosclerosis of the pulmonary artery and signs of congestive heart failure. These lesions help to explain the mechanism by which extreme spinal deformities cause death.

The investigations of Chapman and his co-workers<sup>1</sup> indicated that the diminution in the size of the lungs and the reduction in the vital capacity with deficient oxygenation of the blood throw an increasing strain on the right side of the heart. Since the pressure in the pulmonary artery cannot as yet be measured, the evidence for increased pressure in the pulmonary vascular tree is indirect and is furnished by the hypertrophied and/or dilated right side of the heart and the atheroma of the pulmonary artery. In the absence of any etiologically important lesions, such as severe pulmonary arteriolar sclerosis, one must, for the present at least, fall back on the concept of a purely mechanical effect on respiratory function to explain the pulmonary hypertension and the failure of the right side of the heart.

#### SUMMARY

The clinical and pathologic characters of 5 cases of pulmonocardiac failure in extreme spinal deformity are described.

The significant pathologic lesions are the result of pulmonary hypertension, which eventually leads to right-sided heart failure and appears to be due to mechanical interference with respiratory function.

Prof. William Boyd gave me permission to report these cases.

# EXCRETION OF COPROPORPHYRIN IN HEPATIC DISEASE

## I. CORRELATION OF URINARY AND FECAL EXCRETION WITH PARENCHYMATOUS HEPATIC DAMAGE

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Porphyrins are red pigment substances, the chemical structure of which is based on a ring formed by four pyrrole nuclei which are connected in the form of a closed system by four methine bridges. It has long been recognized<sup>1</sup> that small amounts of porphyrin are excreted normally in the urine of healthy persons and that these amounts may be increased in the urine of patients suffering from a variety of diseases. Porphyrinuria (increased proportion of porphyrin in the urine) has been described as accompanying many forms of hepatic disease,<sup>2</sup> including cinchophen hepatitis, atrophic cirrhosis, obstructive jaundice, chronic passive congestion, lymphosarcoma of the liver, infectious icterus, melanosarcoma of the liver, hemolytic icterus and hemochromatosis.

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From the Division of Medicine (Dr. Snell), the Mayo Clinic.

Abstract of a portion of the thesis submitted by Dr. Samuel Nesbitt to the faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Doctor of Philosophy in medicine.

1. (a) Garrod, A. E.: On the Occurrence and Detection of Haematoporphyrin in the Urine, *J. Physiol.* **13**:598-620, 1892. (b) Günther, H.: Die Hämatoporphyrurie, *Deutsches Arch. f. klin. Med.* **105**:89-146 (Dec. 20) 1911.

2. Dobriner, K.: Urinary Porphyrins in Disease, *J. Biol. Chem.* **113**:1-10 (Feb.) 1936. Garrod, A. E.: Haematoporphyrin in Normal Urine, *J. Physiol.* **17**:349-352, 1894; The Urinary Pigments in Their Pathological Aspects, *Lancet* **2**:1323-1331 (Nov. 10) 1900; *Inborn Errors of Metabolism*, ed. 2, London, H. Froude, Hodder & Stoughton, 1923, p. 136. Günther, H.: Haematoporphyrine, in Schittenhelm, A.: *Handbuch der Krankheiten des Blutes und der blutbildenden Organe*, Berlin, Julius Springer, 1925, vol. 2, pp. 622-673. Tropp, C., and Penew, L.: Quantitativen klinische Harnporphyrinuntersuchungen: II. Lebercirrhosen, Hepatopathien (ausser Cirrhosen), Tuberkulose und andere Krankheiten, *Deutsches Arch. f. klin. Med.* **180**:411-422, 1937. Vigliani, E. C., and Libowitzky, H.: Ueber Porphyrine im Harn und im Kot, *Klin. Wchnschr.* **16**:1243-1245 (Sept. 4) 1937. von Zeynek, R.: Zur Frage des einheitlichen Hämatins und einige Erfahrungen über die Eisenabspaltung aus Blutfarbstoff, *Ztschr. f. physiol. Chem.* **49**:472-481, 1906. Garrod.<sup>1a</sup>

It has been suggested that porphyrinuria observed in the presence of various other diseases and toxic states is caused by associated hepatic damage or dysfunction.<sup>3</sup> Much evidence has accumulated which would indicate that porphyrin arises in the body during the process of hemopoiesis,<sup>4</sup> rather than during the destruction of hemoglobin, as had been supposed formerly, and that the coproporphyrin which is excreted in the urine and bile represents, first, an amount of isomeric series I porphyrin which arises as a useless by-product of the main synthesis and, second, any isomeric series III porphyrin which has not been utilized in the production of hemoglobin. The rate of excretion of coproporphyrin in the urine and bile depends on several factors, chief of which are the rate of production of the porphyrin which is to be excreted and the efficiency of the liver in disposing of the material. The liver furnishes the most important means of excretion of porphyrins; the kidneys usually excrete only a small fraction of total porphyrins.<sup>5</sup> Various investigators<sup>6</sup> have in fact attempted to devise

3. Althausen, T. L.: Zur Frage der Leberschädigung bei der akuten Porphyrinurie, *Klin. Wchnschr.* **10**:1016-1017 (May 30) 1931. Fikentscher, R.: Untersuchungen über den Harnporphyrinspiegel bei Schwangerschaftstoxikosen, insbesondere bei Leberstörungen, *Ztschr. f. Geburtsh. u. Gynäk.* **111**:210-217, 1935. Herold, L.: Das Verhalten der Porphyrinausscheidung bei der Hyperemesis gravidarum und ihre Beziehung zur Leberfunktion, *Arch. f. Gynäk.* **159**:35-40, 1935. Kapp, E. M., and Coburn, A. F.: Studies on the Excretion of Urinary Porphyrin in Rheumatic Fever, *Brit. J. Exper. Path.* **17**:255-266 (Aug.) 1936; Spectrographic Observations on Urinary Porphyrins: The Nature of a Combined Form of Coproporphyrin Found in Urine, *ibid.* **20**:33-41 (Feb.) 1939. Ravn, J.: Störung der Leberfunktion bei zwei Fällen akuter Porphyrurie nebst einigen Bemerkungen ueber den Begriff Porphyrurie, *Acta psychiat. et neurol.* **10**:459-480, 1935.

4. (a) Dobriner, K.: Porphyrin Excretion in Feces in Normal and Pathological Conditions, *J. Biol. Chem.* **120**:115-127 (Aug.) 1937. (b) Dobriner, K., and Rhoads, C. P.: The Metabolism of Blood Pigments in Pernicious Anemia, *J. Clin. Investigation* **17**:95-103 (Jan.) 1938. (c) Dobriner, K.; Strain, W. H.; Localio, S. A.; Keutmann, H., and Stephens, D. I.: II. Coproporphyrin I Metabolism and Hematopoietic Activity, *Proc. Soc. Exper. Biol. & Med.* **36**:755-756 (June) 1937. (d) Rimington, C.: Porphyrins and Their Relation to Metabolism of Blood Pigments, *Proc. Roy. Soc. Med.* **32**:1268-1275 (Aug.) 1939. (e) Lemberg, R.: Transformation of Haemins into Bile Pigments, *Biochem. J.* **29**:1322-1336, 1935.

5. Dobriner, K., and Rhoads, C. P.: Quantitative Determination of Urinary Coproporphyrin, *New England J. Med.* **219**:1027-1029 (Dec. 29) 1938. Vigliani, E. C., and Waldenström, J.: Untersuchungen über die Porphyrine beim Saturnismus, *Deutsches Arch. f. klin. Med.* **180**:182-192, 1937. Waldenström, J.: Untersuchungen über Harnfarbstoffe, hauptsächlich Porphyrine, mittels der chromatographischen Analyse, *ibid.* **178**:38-49, 1935. Dobriner.<sup>4a</sup>

6. Brugsch, J. T.: Untersuchungen des quantitativen Porphyrinstoffwechsels beim gesunden und kranken Menschen, *Ztschr. f. d. ges. exper. Med.* **95**:471-

methods for producing transient porphyrinuria by one means or another as a test of hepatic function.

#### NATURE OF THE PRESENT STUDY

The present investigation was undertaken to learn whether the degree of porphyrinuria present or the ratio of porphyrins excreted in the urine to porphyrins excreted in the feces in cases of disease of the liver had any relation to the extent of parenchymatous hepatic damage. For this purpose a series of 17 cases was selected. These represented a variety of hepatic diseases and degrees of hepatic damage ranging from mild to severe. Space does not permit an account of the individual cases, some details of which are presented in the table. The patients were maintained on a completely meat-free diet throughout the period of observation. Daily determinations of the amount of coproporphyrin excreted in the urine and feces of these patients were made, often over extended periods because of the extensive fluctuation in values which sometimes occurred from day to day. For this purpose a fluorophotometric method was devised<sup>7</sup> which consisted essentially of successive extraction of a measured portion of a specimen of the urine or stool with an acetic acid-ether mixture and 5 per cent hydrochloric acid, purification of the acid solution by the addition of sodium acetate until it was neutral when tested with congo red paper, repetition of the extraction process and, ultimately, measurement of the amount of coproporphyrin in the final acid extract. This last-named process was accomplished by determination by means of a fluorophotometer<sup>8</sup> of the intensity

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481, 1935; Untersuchungen des quantitativen Porphyrinstoffwechsels beim gesunden und kranken Menschen: III. Der Porphyrinstoffwechsel bei Lebererkrankungen, *ibid.* **95**:493-507, 1935. Franke, K.: Klinische und lebendmikroskopische Untersuchungen der gestörten Leberfunktion: II. Untersuchungen über beginnende Leberschädigungen unter besonderer Berücksichtigung der Porphyrinausscheidung im Urin, *Ztschr. f. klin. Med.* **130**:222-234, 1936. Franke, K., and Fikentscher, R.: Die Bedeutung der quantitativen Porphyrinbestimmung mit der Lumineszenzmessung für die Prüfung der Leberfunktion und für Ernährungsfragen, *München. med. Wchnschr.* **1**:171-172 (Jan. 31) 1935. Kaunitz, H.: Ueber Porphyrinurie nach Hämoglobinbelastung, *Ztschr. f. klin. Med.* **133**:552-562, 1938. Keys, A., and Brugsch, J. T.: Porphyrins and Porphyrinemia, *Am. J. Digest. Dis.* **5**:49-50 (March) 1938.

7. Nesbitt, S., and Mason, H. L.: Unpublished data.

8. Brugsch, J. T., and Keys, A.: Quantitative Separation and Estimation of Various Porphyrins in Biological Materials, *Proc. Soc. Exper. Biol. & Med.* **38**:557-560 (May) 1938. Fikentscher, R.: Quantitative Porphyrin-Bestimmung durch Lumineszenzintensitätsmessung mit dem Stufenphotometer, *Biochem. Ztschr.* **249**:357-269, 1932. Stevens, D. S., and Turner, W. J.: The Measurement of Fluorescence Intensity by Photo-Electric Means, *J. Lab. & Clin. Med.* **23**:81-84 (Oct.) 1937.

of the red fluorescence of the extract in ultraviolet light as compared with the fluorescence of a known standard. In determinations of the fecal excretion of coproporphyrins additional procedures for purification always are necessary to remove porphyrins other than coproporphyrin; this involves several extractions of the porphyrin solution in 0.2 per cent hydrochloric acid with chloroform. By this method normal values for coproporphyrin in the urine were found to range from 0 to 70 micrograms in twenty-four hours, although occasionally values as high as

*Clinical and Laboratory Data in Seventeen Cases of Hepatic Disease*

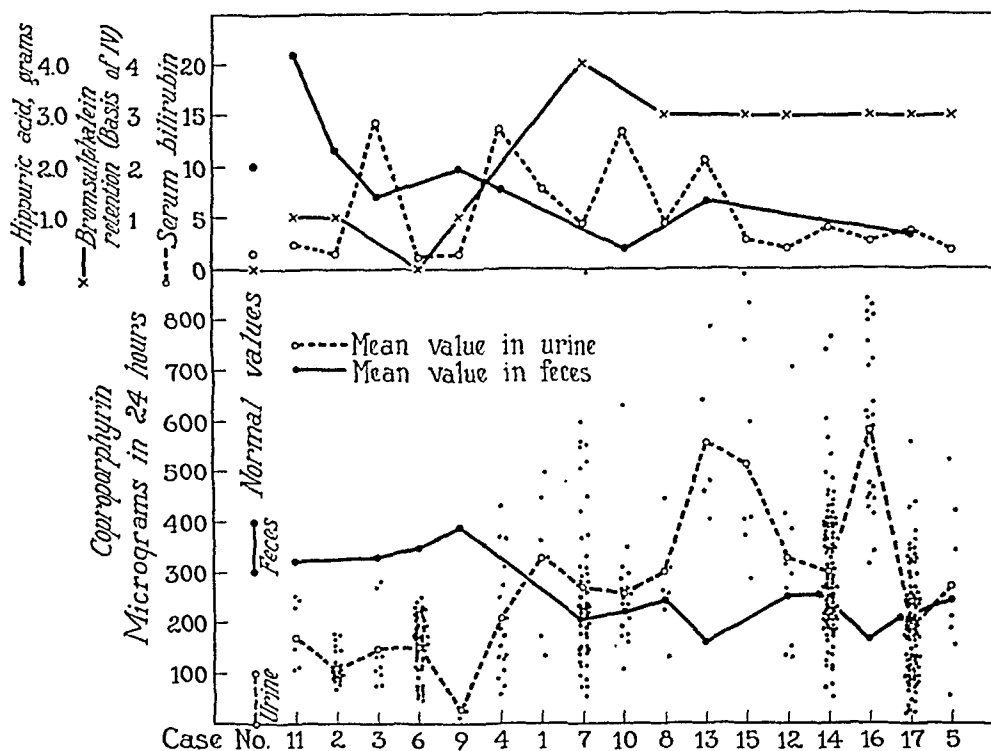
Case No.	Diagnosis	Days Observed	Excretion of Coproporphyrin, Micrograms		In Feces, Mean	Urinary-Fecal Ratio of Excretion
			In Urine			
			Range	Mean		
1	Obstructive biliary cirrhosis; stricture of common duct .....	6	132-500	350	.....	.....
2	Obstructive biliary cirrhosis; stone in common duct .....	21	50-178	105	.....	.....
3	Hepatitis (syphilitic); biliary cirrhosis; stone in common duct .....	9	76-280	155	312	0.49
4	Epidemic hepatitis .....	17	58-248	220	.....	.....
5	Hepatic metastasis from carcinoma of rectum .....	8	190-520	275	246	1.14
6	Fatty liver (gastrocolic fistula) .....	51	60-240	155	350	0.44
7	Subacute atrophy of liver.....	49	115-600	275	203	1.40
8	Atrophic cirrhosis of liver (unknown causation) .....	6	135-445	300	255	1.20
9	Atrophic cirrhosis of liver (unknown causation) .....	4	18-39	33	395	0.084
10	Atrophic cirrhosis of liver (unknown causation) .....	17	100-630	270	208	1.3
11	Latent or compensated alcoholic cirrhosis .....	6	106-242	175	310	0.56
12	Alcoholic cirrhosis .....	10	53-417	350	245	1.4
13	Alcoholic cirrhosis .....	5	400-782	570	172	3.3
14	Alcoholic cirrhosis .....	93	100-600	300	248	1.2
15	Alcoholic cirrhosis .....	9	290-844	510	.....	.....
16	Alcoholic cirrhosis .....	48	414-838	595	165	3.6
17	Alcoholic cirrhosis .....	92	21-560	200	205	0.99

100 micrograms were encountered. The normal range of coproporphyrin in the feces was from 300 to 400 micrograms in twenty-four hours. The urinary-fecal ratio varied from 0.07 to 0.24. Coproporphyrin was isolated from the urine in 10 cases, and its isomeric type was identified by determination of the melting point.<sup>9</sup> In many instances the amount of coproporphyrin present in ascitic fluid and also in the fluid obtained on thoracentesis was determined, and although an appreciable quantity was present in each instance, the amounts in these reservoirs were not sufficient to constitute factors to be considered in the loss of porphyrin from the body.

9. Nesbitt, S.: Unpublished data.

## CORRELATION OF LABORATORY DATA AND CLINICAL OBSERVATIONS

In the figure are represented the many determinations of coproporphyrin as excreted in twenty-four hour specimens of urine in each case; the mean value has been indicated in each instance. In most cases the mean value for coproporphyrin excreted in the feces has been included. Whenever possible, certain laboratory determinations, including those of serum bilirubin, retention of bromsulphalein and excretion of hippuric acid, have been represented in order to furnish, so far as possible, an estimation of the degree of parenchymatous hepatic damage



Excretion of coproporphyrin in the urine and feces in 17 cases of hepatic disease.

present in the individual case. An evaluation of the clinical course of the disease and study of material at necropsy in some instances provided additional information as to the functional capacity of the liver.

*An Illustrative Single Case.*—We have selected 1 of the 17 cases for consideration in order to illustrate in what manner the aforementioned data were correlated for the purpose of estimating the degree of parenchymatous hepatic damage in relation to the value for the excretion of porphyrins.

In case 17 (table) the patient presented a history of long addiction to alcohol and jaundice and ascites of several months' duration. On physical examination pulsating telangiectasis, icterus, ascites, dependent edema and development of a



collateral circulation were found. The value for serum bilirubin was elevated (3.6 mg. per hundred cubic centimeters), and the reaction to the van den Bergh procedure was direct. A macrocytic type of anemia was noted. The excretion of hippuric acid was 0.72 Gm. in four hours, after the administration of 6 Gm. of sodium benzoate. Results of the bromsulphalein test showed retention of dye of grade 3 (retention of dye graded on the basis of 1 to 4). Peritoneoscopic examination afforded confirmatory evidence as to the correctness of the original diagnosis of atrophic cirrhosis. The course of illness while the patient was under observation also established the extreme extent of parenchymatous hepatic damage. The prothrombin clotting time remained elevated despite parenteral and oral administration of synthetic preparations which possessed vitamin K activity; the value for plasma protein continued to decrease in spite of every effort to sustain it, including intravenous reinfusion of the patient's ascitic fluid. There were also numerous episodes of acute hepatic insufficiency, as evidenced by coma. When the values for coproporphyrin excreted in the twenty-four hour specimens of urine are examined (figure) it is seen that many of them lie well within the normal range. Most of the values, however, are abnormally elevated, to as high as 560 micrograms, and the mean value of these determinations is found to be 200 micrograms, a value considerably higher than values in the normal range. The average daily quantity of coproporphyrin excreted in the feces of this patient for a period of five days was 205 micrograms, an amount definitely below normal. Thus it is seen that the urinary-fecal ratio of the excretion of coproporphyrin in this instance is 0.99, a marked relative increase over the usual value, which ranges from 0.07 to 0.24.

*Correlative Factors.*—On the basis of a consideration of the data as presented in the figure it at once becomes apparent that the amount of coproporphyrin excreted in the urine in each case from day to day is distributed over a wide range which usually includes some normal values despite severe hepatic damage, so that single determinations may not be considered as informative. However, in all the cases of hepatic disease studied with but a single exception (case 9) most of the values for coproporphyrin excreted in the urine are well above the normal range and the mean value of any given series of determinations seems to be a fair index of the degree of hepatic damage present in the particular case.

As might be expected, there also appears to be a correlation between the amount of coproporphyrin excreted in the feces and the degree of hepatic damage present. In cases 11, 3, 6 and 9, which are representative of moderate hepatic damage, the patients excreted normal amounts of coproporphyrin in the stool, whereas in all the other instances in which determinations of coproporphyrin in feces were carried out, and which are representative of more severely damaged livers, the patients excreted reduced amounts of coproporphyrin in the feces.

*Illustrative Laboratory Data.*—In case 11 the patient had latent or compensated alcoholic cirrhosis but did not have ascites. The liver was but moderately damaged, as indicated by a slightly elevated value for

serum bilirubin, by a direct reaction to the van den Bergh procedure and by retention of dye of grade 1. The excretion of hippuric acid was normal, and when the patient was seen ten months later the reaction to the test for bilirubin in the serum was indirect and there was no retention of dye. The mean value for a series of estimations of the content of coproporphyrin in the feces of this patient was normal.

In case 2 stone of the common bile duct was present, and the patient showed some degree of biliary cirrhosis at the time of operation. A moderate degree of hepatic damage was present, as indicated by the direct reaction to the van den Bergh test and retention of dye of grade 1; the excretion of hippuric acid was just within normal limits. The mean value for coproporphyrin in the urine was just above normal limits.

In case 3, in which syphilitic hepatitis, stone of the common bile duct and biliary cirrhosis were present, the patient had a large nodular liver; the excretion of hippuric acid was moderately decreased. In this instance the mean value for coproporphyrin excreted in the urine was elevated moderately and the amount excreted in the feces was normal.

In case 6 the patient had a gastrocolic fistula. A diagnosis of fatty liver was made on the basis of nutritional disturbance and was confirmed at operation, although little parenchymatous damage could be demonstrated by the usual laboratory methods. The mean value for coproporphyrin excreted in the urine was only moderately elevated, and the value for coproporphyrin excreted in the feces was normal.

In case 9 the patient had atrophic cirrhosis and presented the clinical picture of cirrhosis, but the liver was functioning fairly well, as was evidenced by retention of dye of only grade 1 and an excretion of hippuric acid of 1.96 Gm. In fact, this man presented an interesting problem in differential diagnosis between constrictive pericarditis and cirrhosis of the liver until determinations of venous pressure had shown normal values and the liver had been visualized by peritoneoscopy. In this instance the mean values for coproporphyrin excreted both in the urine and in the feces were well within normal limits. The patient is gradually improving at the time of this report (June 1941).

In case 4, in which epidemic, or infectious, hepatitis was present, there was a considerable degree of parenchymatous hepatic damage, as evidenced by the elevated content of bilirubin in the serum, the direct reaction to the van den Bergh procedure, an excretion of hippuric acid of 1.52 Gm. and an excretion of galactose of 4.2 Gm. In this instance the mean value for coproporphyrin excreted in the urine was elevated slightly more than it had been in any of the foregoing cases, being approximately 220 micrograms.

In case 1 the patient had stricture of the common bile duct and presented a considerable degree of obstructive biliary cirrhosis, as observed at the time of operation. The mean value for coproporphyrin excreted in the urine was more than 300 micrograms.

In case 7 the patient had subacute atrophy and had sustained a considerable degree of parenchymatous hepatic damage, as evidenced by a direct reaction to the van den Bergh procedure, with a value for serum bilirubin of 4.3 mg. per hundred cubic centimeters, a persistently elevated prothrombin clotting time and retention of dye of grade 4. The excretion of coproporphyrin in the urine was considerably increased, whereas the values for coproporphyrin in the feces were low.

In cases 8 and 10 the patients had atrophic cirrhosis and the livers undoubtedly had sustained considerable parenchymatous damage, as shown by the clinical observations and by laboratory data pertaining to hepatic function. The values for the excretion of coproporphyrin in the urine and feces in these 2 cases are seen in the figure to correspond roughly to analogous values in case 7.

In cases 12, 13, 14, 15, 16 and 17 the condition of advanced alcoholic cirrhosis with extreme degrees of parenchymatous hepatic damage, as evidenced clinically and by laboratory tests, is represented. Case 17, which has been described in some detail, is representative of this group as a whole. It is in this particular group of cases that the highest mean values for coproporphyrin excreted in the urine were found and that the lowest values for coproporphyrin excreted in the feces were encountered. Surprisingly enough, the 1 patient of this group (case 16) who did well and who continued to improve was the one who excreted the greatest quantities (on a mean basis) of coproporphyrin in the urine and whose values for coproporphyrin in the feces were low. The patient who had carcinoma of the rectum with extensive metastasis to the liver (case 5) exhibited both clinical and laboratory evidence of severe hepatic insufficiency, and this condition was confirmed at necropsy.

#### SUMMARY AND CONCLUSIONS

In 5 cases (11, 2, 3, 6 and 9) in which evidence of mild hepatic damage was presented the mean value for coproporphyrin excreted in the urine during twenty-four hours was between 100 and 200 micrograms in 4 instances and was well within normal limits in the other case. In 4 of these cases the excretion of coproporphyrin in the feces was within normal limits. In 5 cases (4, 1, 7, 10 and 8) in which evidence of moderately severe parenchymatous hepatic damage was presented the mean value for the excretion of coproporphyrin in the urine ranged between 200 and 300 micrograms per twenty-four hours with a single exception, in which the excretion was 350 micrograms per twenty-four hours. In 3 of these cases (7, 10 and 8) the excretion of

coproporphyrin<sup>1</sup> in the feces was diminished; it ranged between 200 and 255 micrograms per twenty-four hours. In 7 cases (13, 15, 12, 14, 16, 17 and 5) in which there was a severe degree of parenchymatous hepatic damage the patients were found with 2 exceptions to have a mean value for excretion of coproporphyrin in the urine which ranged from 300 to 600 micrograms per twenty-four hours. The 2 excepted patients had lower values of 200 and 275 micrograms, respectively. The content of coproporphyrin excreted in the feces of 6 of these patients was found to be diminished and ranged from 160 to 260 micrograms per twenty-four hours. It would seem that among patients suffering from various diseases of the liver the degree of porphyrinuria present and particularly the urinary-fecal ratio of the excretion of coproporphyrin are fair indexes of the extent of parenchymatous hepatic damage present at the time of investigation. The data on the excretion of coproporphyrin are not necessarily of prognostic value, as shown by the occasional recovery of patients in whom the urinary-fecal ratio of such excretion was much disturbed.

NOTE.—Since this work was completed a recently reported investigation, the results of which are in accord with our observations, has come to our attention.<sup>10</sup>

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10. Localio, S. A.; Schwartz, M. S., and Gannon, C.: The Urinary/Fecal Coproporphyrin Ratio in Liver Disease, *J. Clin. Investigation* **20**:7-11 (Jan.) 1941.

# EXCRETION OF COPROPORPHYRIN IN HEPATIC DISEASE

## II. URINARY AND FECAL EXCRETION IN BILIARY OBSTRUCTION

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It has been suggested by various workers that porphyrin concerned in body metabolism arises during the process of formation rather than destruction of hemoglobin<sup>1</sup> and that the rate of excretion of coproporphyrin in the urine and bile depends chiefly on the rate of production of porphyrin to be excreted (a series I isomer arising as a useless by-product and any series III isomer not immediately utilized in hemopoiesis) and the efficiency of the liver, which is the more important organ involved in excretion of porphyrin.<sup>2</sup> The kidneys normally excrete a small fraction of the total porphyrin excreted, but in the event of hepatic damage they excrete increased amounts, a mechanism similar to that for the excretion of bile pigments. It has been claimed that in

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Abstract of a portion of the thesis submitted by Dr. Nesbitt to the faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Doctor of Philosophy in medicine.

1. (a) Dobriner, K.: Porphyrin Excretion in the Feces in Normal and Pathological Conditions, *J. Biol. Chem.* **120**:115-127 (Aug.) 1937. (b) Dobriner, K., and Rhoads, C. P.: The Metabolism of Blood Pigments in Pernicious Anemia, *J. Clin. Investigation* **17**:95-103 (Jan.) 1938. (c) Dobriner, K.; Strain, W. H.; Localio, S. A.; Keutmann, H., and Stephens, D. I.: II. Coproporphyrin I Metabolism and Hematopoietic Activity, *Proc. Soc. Exper. Biol. & Med.* **36**:755-756 (June) 1937. (d) Rimington, C.: Porphyrins and Their Relation to the Metabolism of Blood Pigments, *Proc. Roy. Soc. Med.* **32**:1268-1275 (Aug.) 1939. (e) Lemberg, R.: Transformation of Haemins into Bile Pigments, *Biochem. J.* **29**:1322-1336, 1935.

2. (a) Dobriner, K., and Rhoads, C. P.: The Quantitative Determination of Urinary Coproporphyrin, *New England J. Med.* **219**:1027-1029 (Dec. 29) 1938. (b) Watson, C. J.: Concerning the Naturally Occurring Porphyrins: I. The Isolation of Coproporphyrin I from the Urine in a Case of Cincophen Cirrhosis, *J. Clin. Investigation* **14**:106-109 (Jan.) 1935; (c) Concerning the Naturally Occurring Phorphyrins: IV. The Urinary Porphyrin in Lead Poisoning as Contrasted with that Excreted Normally and in Other Diseases, *ibid.* **15**:327-334 (May) 1936. Dobriner.<sup>1a</sup>

complete obstruction of the common bile duct the total excretion of coproporphyrin is not altered but that coproporphyrin practically or entirely disappears from the feces and appears in greatly increased amounts in the urine<sup>3</sup> and occurs in the blood serum, which normally does not contain any coproporphyrin.<sup>4</sup>

Certain experimental procedures have been carried out which lend support to such a mechanism of excretion of porphyrin.<sup>5</sup> Lageder<sup>5b</sup> studied the bile pigment values along with the urinary excretion of porphyrin by rabbits and concluded that the porphyrinuria which developed after ligation of the common bile duct was not explainable simply as an overflow but that some correlation existed between the porphyrinuria and the degree of damage of the liver cells. This is borne out by the fact that Watson<sup>2b</sup> in 3 cases of obstruction of the common duct (stone) noted a definite but only moderate increase in the urinary coproporphyrin, which was much less than the porphyrin in the urine in a case of cinchophen cirrhosis. On the other hand, the urine of a patient who had hepatic insufficiency due to advanced hepar lobatum did not contain any trace of coproporphyrin. This might indicate that more than one factor operates in the excretion of coproporphyrin by the liver.

In order to investigate the urinary-fecal ratio of coproporphyrin excretion associated with obstruction of the common bile duct, 6 cases were selected which represented various degrees of obstructive jaundice as well as various degrees of parenchymatous hepatic damage caused by neoplasm, stricture of the common duct or calculus of the common duct. The relation of the amount of coproporphyrin excreted in the urine in these cases as determined in the twenty-four hour specimens to that excreted in the feces is demonstrated graphically in figures 1 through 6. In these cases the patients were studied before and after operative procedures which were carried out to restore continuity of the bile

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4. Boas, I.: Ueber das Vorkommen von Protoporphyrin im Harn, *Klin. Wchnschr.* **12**:589-591 (April 15) 1933.

5. (a) Mathews, F. P.: Photosensitization and the Photodynamic Diseases of Man and the Lower Animals, *Arch. Path.* **23**:399-429 (March) 1937. (b) Lageder, K.: Klinische Porphyrinuntersuchungen mit einer quantitativen spektroskopischen Methode, *Arch. f. Verdauungskr.* **56**:237-256 (Nov.) 1934. (c) Smetana, H.: Studies on Photodynamic Action: II. The Fate of Hematoporphyrin After Parenteral Administration; III. The Influence of Sensitizer on Photooxidation of Tissues, *J. Biol. Chem.* **125**:741-751 (Oct.) 1938. (d) Eldahl, A.: Porphyrines and Clinical Methods for Their Demonstration, *Acta med. Scandinav.* **97**:538-546, 1938.

passage. It must be realized that it is difficult or impossible to be sure of a completely obstructed bile passage because duodenal drainage is not entirely reliable, and one must be guarded in drawing conclusions from data derived from surgical patients such as these because of the many complicating factors present, for example, the anesthetic agent employed, most anesthetic substances being known to affect excretion of porphyrin.

Case 1 (fig. 1) illustrates the values which might be expected in the instance of obstruction of the common duct with little or no parenchymatous hepatic damage. The patient presented clinical evidence of obstruction for only two weeks. The obstruction was found at operation to be caused by carcinoma of the head of the pancreas. Before operation the stools did not contain any coproporphyrin and the urinary excretion of coproporphyrin was elevated. After cholecystogastrostomy the patient excreted normal amounts of coproporphyrin in the stool and the urinary excretion fell within normal limits.

In case 2 (fig. 2), in which obstruction of the common duct was caused by carcinoma of the pancreas, the course was similar, although in this instance, even before operation, considerable coproporphyrin was excreted in the feces and the urinary excretion was not markedly elevated, perhaps indicating that obstruction was not complete.

Case 3 (fig. 3), in which obstruction of the common bile duct was caused by stricture, illustrates the usual elevated excretion of coproporphyrin in the urine, there being a small amount in the feces. Subsequent to hepaticoduodenostomy the excretion of coproporphyrin in the feces increased, but by the time the patient was dismissed the urinary excretion had not quite returned to within normal limits, perhaps because of parenchymatous hepatic damage which was known to exist.

Case 4 (fig. 4), in which there was a calculus in the common duct, illustrates what might be expected to occur in the instance of partial or intermittent biliary obstruction. The urinary excretion of coproporphyrin varied from day to day from high normal values to only moderately elevated levels, and considerable quantities of coproporphyrin were excreted in the stool. Subsequent to removal of the calculus from the common duct there was but little change in excretion of porphyrin, there being a slight increase in the fecal excretion of coproporphyrin and a tendency for the urinary excretion to remain at a lower level.

Case 5 (fig. 5) is that of a woman who had obstruction of the common bile duct by carcinoma of the duct itself. Despite the fact that bile was not obtained by duodenal drainage, there was an appreciable quantity of coproporphyrin in the stool, which perhaps may mean that some bile did pass through at times. There is evidence that bacteria in the intestine may synthesize coproporphyrin or may produce it from

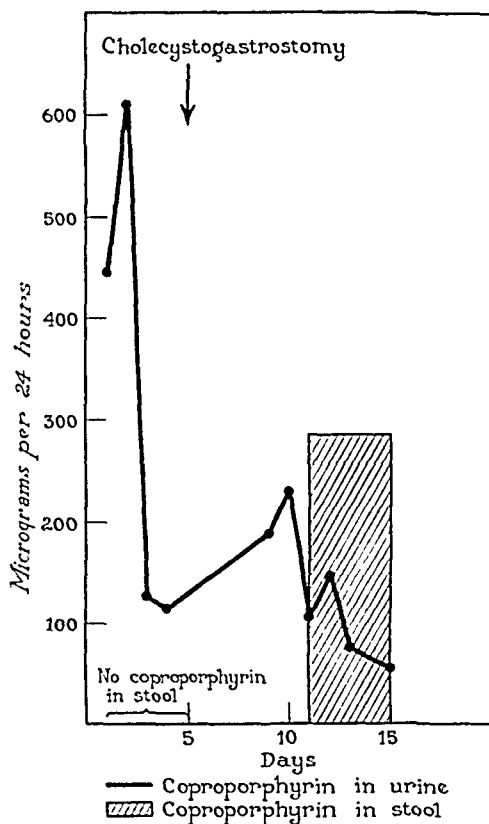


Fig. 1 (case 1).—Urinary and fecal excretion of coproporphyrin before and after relief of biliary obstruction.

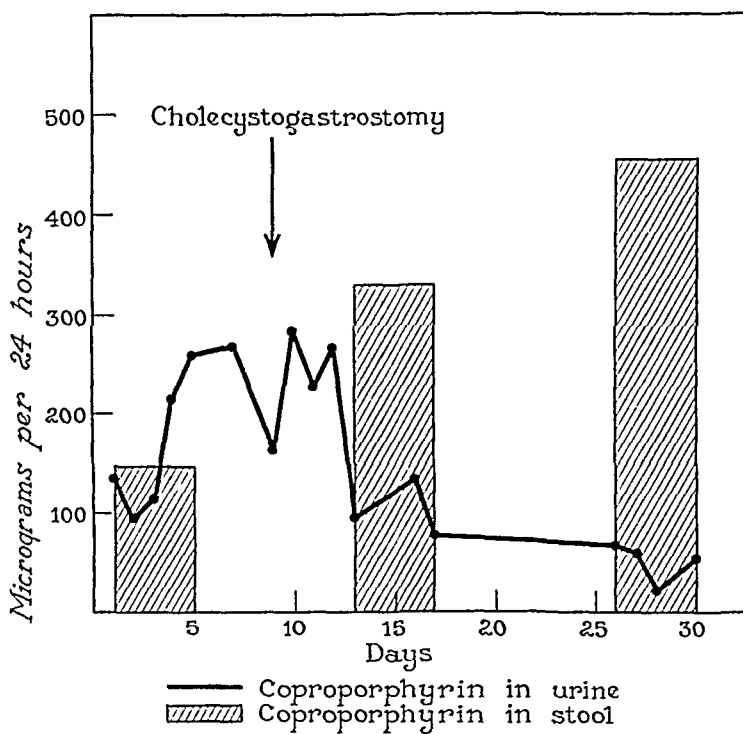


Fig. 2 (case 2).—Urinary and fecal excretion of coproporphyrin before and after relief of biliary obstruction. The obstruction was perhaps not complete.



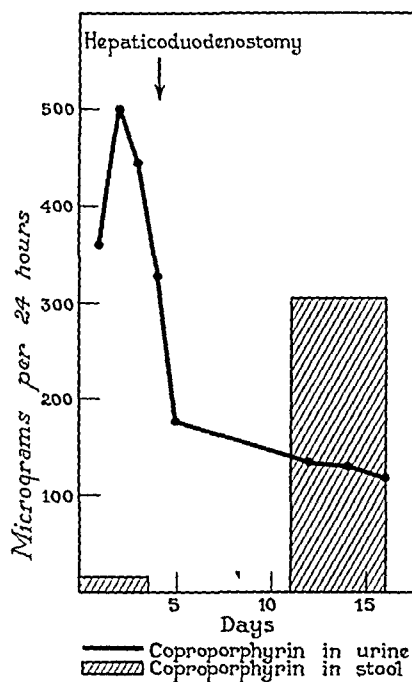


Fig. 3 (case 3).—Urinary and fecal excretion of coproporphyrin before and after relief of biliary obstruction. The failure of the urinary excretion to return to normal may have been due to parenchymatous hepatic damage.

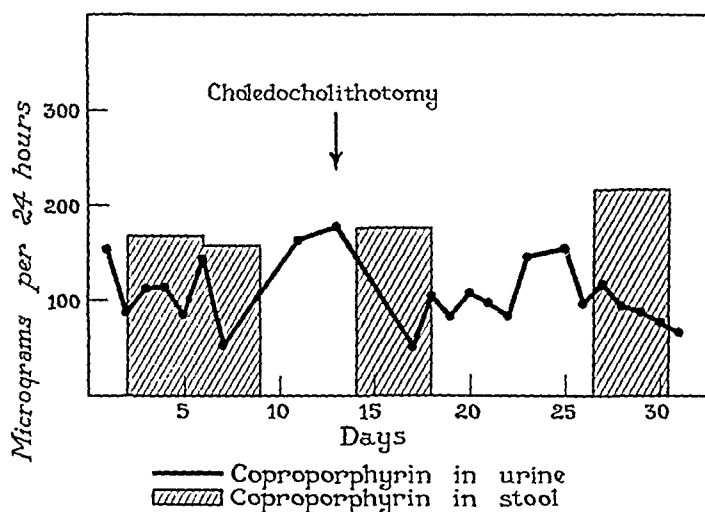


Fig. 4 (case 4).—Urinary and fecal excretion of coproporphyrin before and after relief of partial or intermittent biliary obstruction.

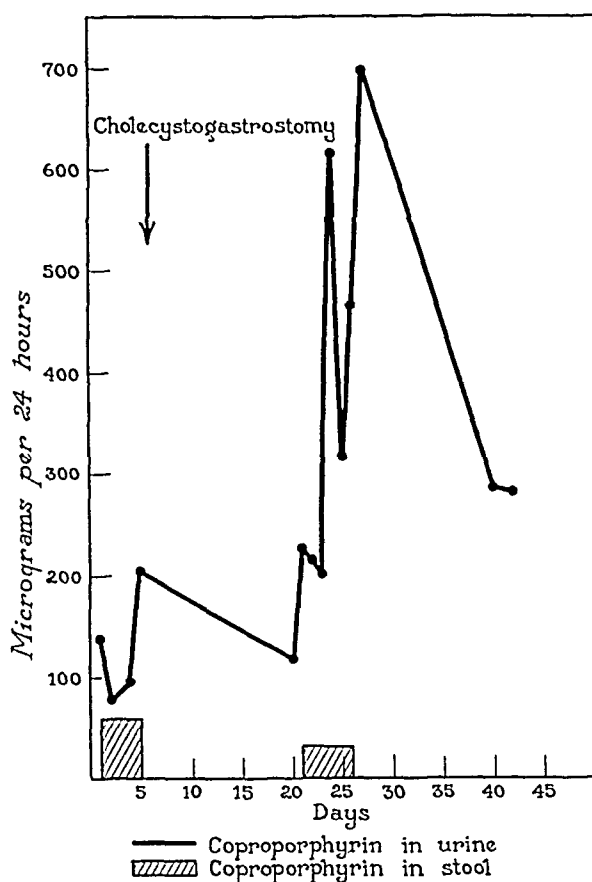


Fig. 5 (case 5).—Urinary and fecal excretion of coproporphyrin before and after relief of biliary obstruction. The increase of urinary excretion and decrease of fecal excretion after operation may have been due to further parenchymatous hepatic damage.

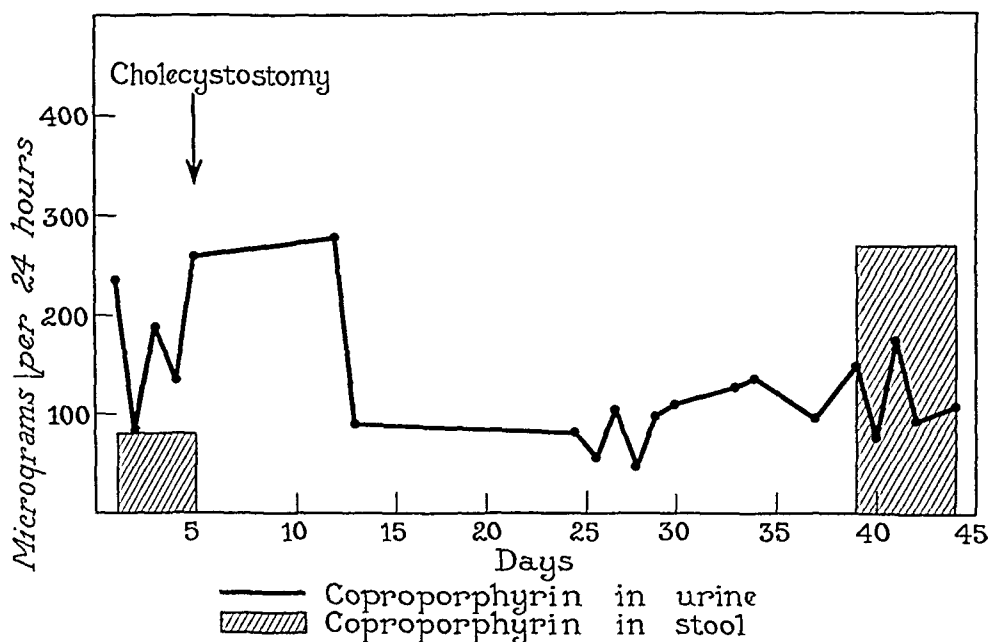


Fig. 6 (case 6).—Urinary and fecal excretion of coproporphyrin. For further explanation see the text.

blood<sup>6</sup> in the intestine, although the idea has been opposed by Kämmerer.<sup>7</sup> If this was so, it would constitute a possible explanation for the unexpected or abnormal amounts of coproporphyrin encountered in the feces of certain of these patients. Subsequent to restoration of the bile passage by means of cholecystogastrostomy, the excretion of coproporphyrin in the urine was increased, whereas that in the feces was decreased. This may be accounted for by the fact that further parenchymatous hepatic damage due to ascending infection, cholangitis or biliary cirrhosis occurred, so that less coproporphyrin was excreted by the liver and the kidneys excreted the excess into the urine. This suggestion is supported by the fact that the patient exhibited every evidence of cholangitis and hepatic insufficiency and that she declined rapidly and died a short time after returning to her home.

Case 6 (fig. 6), in which biliary obstruction was caused by carcinoma of the gallbladder, presented interesting features. The patient, a woman, had an external biliary fistula and was ingesting what bile could be obtained, which probably explains the presence of considerable coproporphyrin in the feces and the fact that the initial urinary excretion was not greatly elevated, a considerable fraction being excreted in the bile through the fistulous tract. After cholecystostomy the amount of coproporphyrin in the feces increased as would be expected, but the urinary excretion did not fall within normal limits, probably because of the extensive hepatic necrosis which was present.

#### SUMMARY AND CONCLUSIONS

The amount of coproporphyrin excreted daily in the urine and feces in 6 cases of obstruction of the common bile duct of varying severity has been estimated both before and after operative procedures which were done to restore the continuity of the bile passage. Before operation the ratio of the amount of coproporphyrin excreted in the urine to the amount excreted in the feces was found to be increased in proportion to the degree of biliary obstruction. Subsequent to operation the urinary-fecal ratio of excretion of coproporphyrin returned to normal or nearly normal or remained elevated, apparently depending on the degree of parenchymatous hepatic damage.

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6. Jakob, A.: Ueber den Abbau von Blutfarbstoff durch Reinkulturen von Bakterien und über die biologische Synthese von "Koproporphyrin III," *Klin. Wchnschr.* **18**:507-508 (April 8) 1939; Ueber den Abbau von Blutfarbstoff zu Porphyrinen durch Reinkulturen von Bakterien und über eine neue biologische Synthese von Koproporphyrin III, *ibid.* **18**:1024-1028 (July 29) 1939.

7. Kämmerer, H.: Ueber den Abbau von Blutfarbstoff zu Porphyrinen durch Reinkulturen von Bakterien und über eine neue biologische Synthese von Koproporphyrin III, *Klin. Wchnschr.* **18**:1323 (Oct. 7) 1939.

# HAMARTIAL NATURE OF THE TUBEROUS SCLEROSIS COMPLEX AND ITS BEARING ON THE TUMOR PROBLEM

REPORT OF A CASE WITH TUMOR ANOMALY OF THE  
KIDNEY AND ADENOMA SEBACEUM

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NEW YORK

Tuberous sclerosis was first described clinically by Bourneville and Brissaud (1880 *et seq*)<sup>1</sup> in feeble-minded children with epilepsy and progressive mental deterioration. This interesting condition has usually been classified among the diseases of the nervous system and has been given only casual attention by general clinicians. Since the term tuberous sclerosis refers primarily to the changes in the brain, the broader term tuberous sclerosis complex is therefore employed to denote the coexistence of homologous changes in other organs, notably the heart, kidneys and skin.

The clinical diagnosis is possible if two or more of the following features can be demonstrated: mental retardation, epilepsy, adenoma sebaceum, phacoma of the retina, multiple mixed tumors (hamartomas) of the kidneys and a familial history of the disease. In some of the reported cases the neurologic features were insignificant or lacking clinically and were discovered first at autopsy.<sup>2</sup> In still other cases the brain apparently presented nothing abnormal despite well marked expressions of the disease in other organs, such as the heart,<sup>3</sup> kidneys<sup>4</sup>

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From the Pathological Laboratory, St. Peter's Hospital, New Brunswick, N. J.

1. (a) Bourneville, D. M.: Contribution à l'étude de l'idiotie. Sclérose tubéreuse des circonvolutions cérébrales; idiotie et épilepsie hémiplegique, Arch. de neurol. **1**:81, 1880. (b) Bourneville, D. M., and Brissaud, E.: Encéphalite ou sclérose tubéreuse des circonvolutions cérébrales, *ibid.* **1**:297, 1880. (c) Bourneville, D. M.: Sclérose cérébrale hypertrophique ou tubéreuse compliquée de méningite, Progrès méd. **3**:129, 1896; (d) Idiotie symptomatique de sclérose tubéreuse ou hypertrophique, *ibid.* **10**:241, 1899; (e) Idiotie et épilepsie symptomatiques de sclérose tubéreuse ou hypertrophique, Arch. de neurol. **10**:29, 1900.

2. Feriz, H.: Ein Beitrag zur Histopathologie der tuberösen Sklerose, Virchows Arch. f. path. Anat. **278**:690, 1930.

3. (a) Rehder, H.: Ein Beitrag zur Kenntnis der sogenannten Rhabdomyome des Herzens, Virchows Arch. f. path. Anat. **217**:174, 1914. (b) Cagnetto, cited by Kaufmann,<sup>4</sup> vol. 1, p. 63.

4. Kaufmann, E.: Lehrbuch der speciellen pathologischen Anatomie, ed. 7-8, Berlin, Walter de Gruyter & Co., 1922, vol. 2, p. 1092.

or skin.<sup>5</sup> The presence of the disease may first be suspected, therefore, by the dermatologist or the urologic surgeon. A case of the latter type is reported here.

#### REPORT OF CASE

F. H., a white girl aged 15, was brought to St. Peter's Hospital Jan. 23, 1933, for treatment of hematuria. Four days previously, while roller skating in follow-the-leader formation, she and several companions lost their balance and fell. Being the last in line, she received their combined weights on her abdomen. She felt pain at once in her back, but when it passed away she resumed play. About four hours later, as she prepared to retire, she passed bloody urine. The following

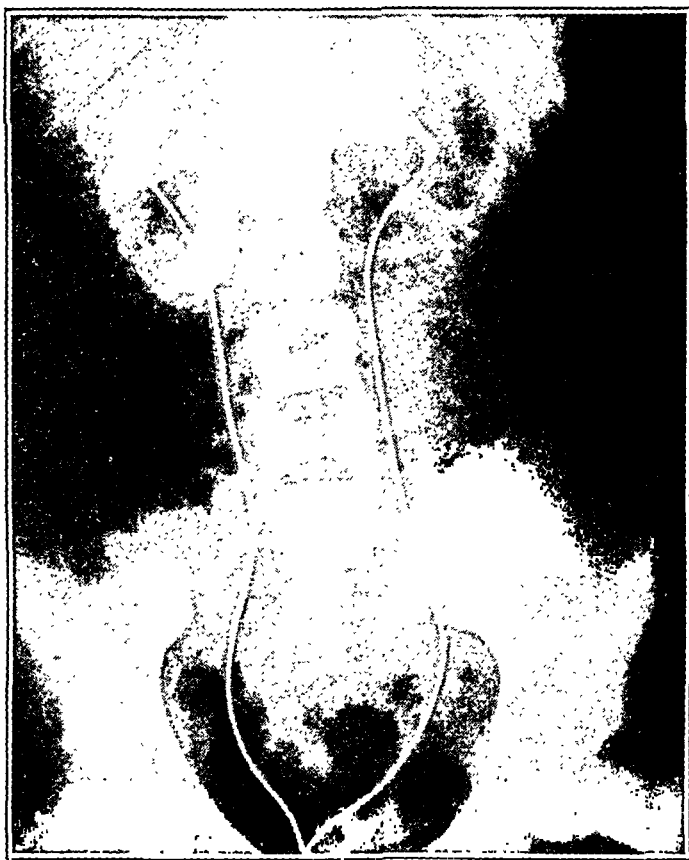


Fig. 1.—The pyelogram made before operation. The dilated right renal pelvis filled unevenly and communicated with an enormous anomalous calix showing a filling defect (blood clot).

morning she voided nearly pure blood and complained of pain in the right groin. She was feverish and vomited several times. From then until the time of admission to the hospital she continued to pass bloody urine intermittently.

A pyelogram (fig. 1) disclosed uneven filling and considerable dilatation of the pelvis and calices of the right kidney. The calix to the lower pole was apparently replaced by a large rounded cavity the size of a plum. This seemed to be outside the kidney within a large mass. The latter had a well defined rounded

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5. Olson, G. M.: Adenoma Sebaceum and Tuberosc Sclerosis, *Arch. Dermat. & Syph.* 6:21 (July) 1922. Pasini, cited by Ferraro and Doolittle.<sup>26</sup>

contour and lay below and mesial to the kidney and overlapped its lower pole. A diagnosis of bleeding tumor was made, and the kidney was resected through a lumbar incision by Dr. R. L. McKiernan.

The specimen removed at operation consisted of the right kidney, which presented a curious ovoid tumor mass springing from its anterior surface just above its lower pole. The mass, roughly one third the size of the kidney itself, was smooth, had rounded overlapping edges and covered the lower part of the kidney like the head of a large mushroom. On section it appeared to be formed by the anomalous expansion of the entire lower anterior segment of the kidney. Its

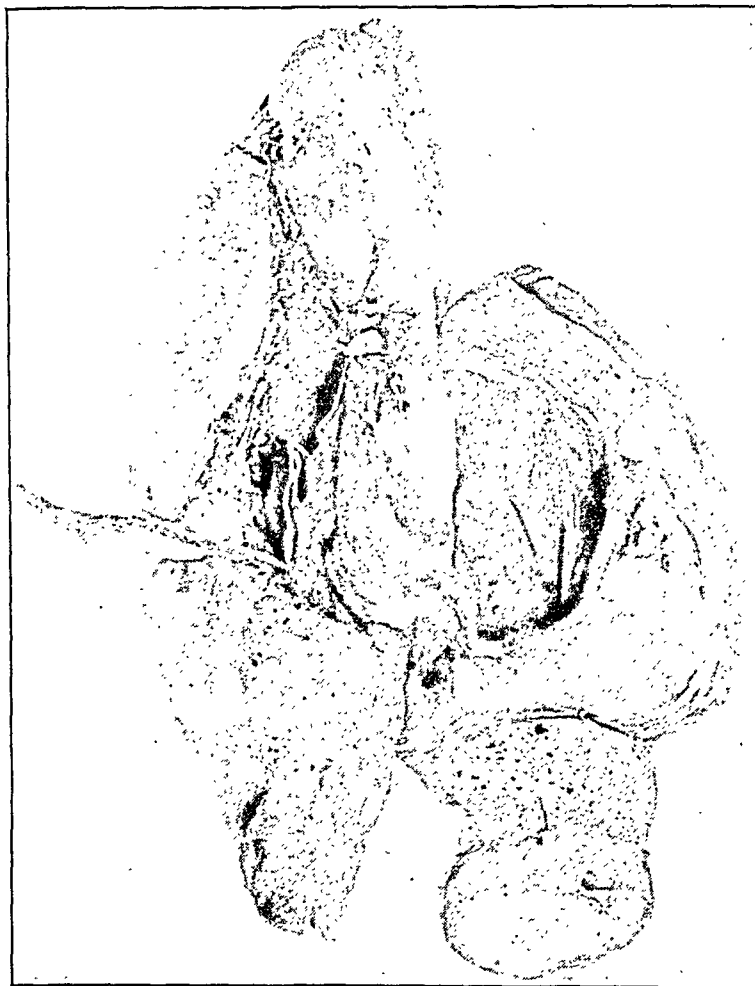


Fig. 2.—The resected right kidney opened to show the large tumor mass, the center of which is formed by the anomalous calix (the blood clot has been removed). Note also the separate smaller tumor mass at the lower pole.

cut surface was yellowish white. Its central portion was hollow and took the form of an anomalous caliceal outgrowth of the renal pelvis. This cavity and the pelvis proper were distended with clotted blood. Its lining was smooth and was continuous with the mucosa of the pelvis (fig. 2). A separate smaller mass, the size of a walnut kernel, was also noted overlying the lower pole of the kidney. It had the same consistency and appearance on section as the larger mass.

Microscopic examination of the tumor masses revealed a mixture of several kinds of unripe tissue of mesenchymal origin. Among these could be defined spindle cell types, smooth muscle, numerous small and large thick-walled blood channels (figs. 3 and 4) and some fat tissue (fig. 5). The cells appeared somewhat atypical but without evidence of active proliferation. Epithelial elements resembling tubules were not encountered. Sections taken from the rest of the kidney revealed a number of minute cysts, probably belonging to the tubular system. They were lined by well formed cuboidal cells with abundant clear cytoplasm.

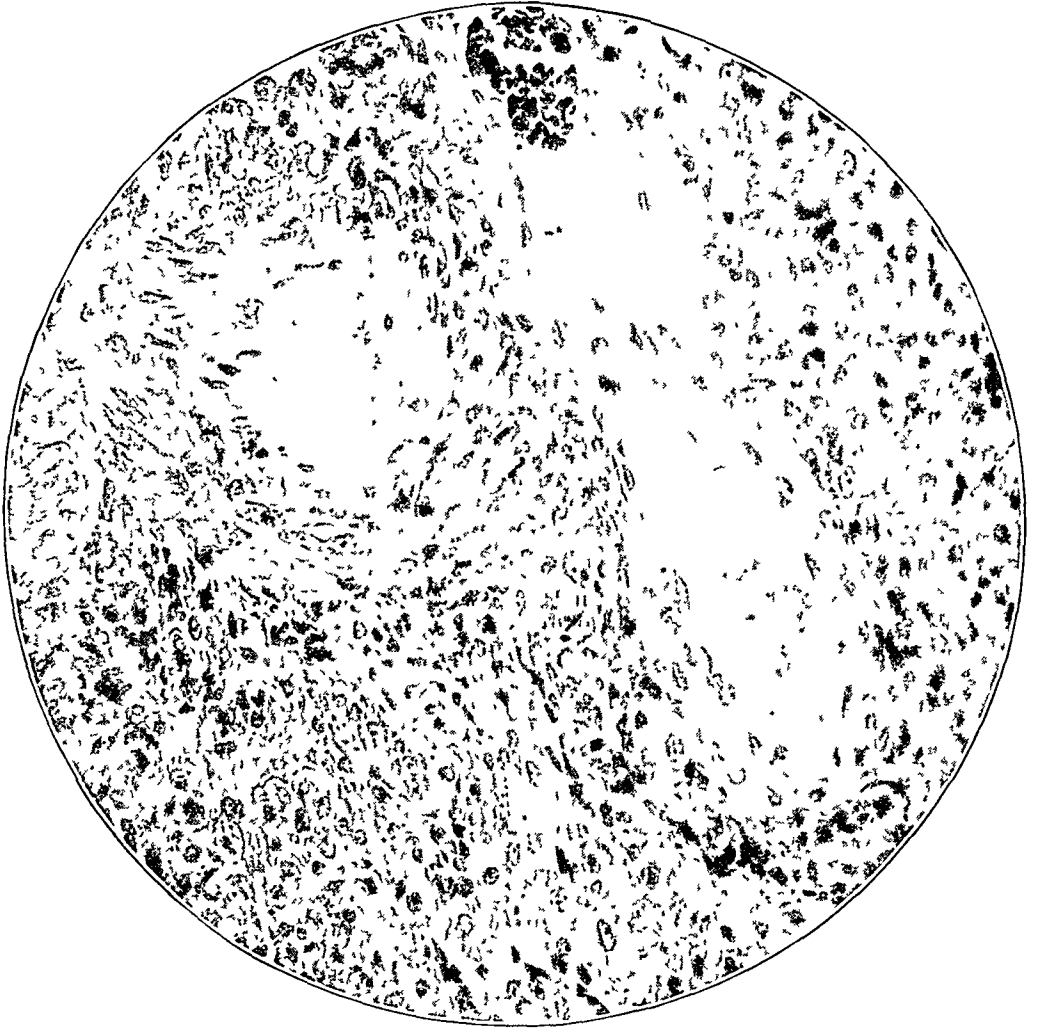


Fig. 3.—A photomicrograph of the hamartoma, showing the primitive mesenchymal cell composition with predominance of vasoformative tissue.

These cysts varied considerably in size and shape and were surrounded by a well developed connective tissue stroma. They appeared to be anomalous rather than obstructive in origin (fig. 6).

The pathologic diagnosis was bleeding hamartoma of the kidney with a caliceal anomaly. The surgical wound healed quickly, and the patient returned home in good condition. Because of the unusual nature of the pathologic findings in the kidney it was suspected that the patient might also harbor other unusual features. She was therefore referred back to the hospital for a general examination.

Over her face and neck were many shiny wartlike nodules, most numerous along the sides and on the tip of her nose and along the nasolabial folds, converging toward her chin. The lesions were characteristic of adenoma sebaceum (fig. 7 *A*). They ranged from pinpoint to matchhead size. Most of them were



Fig. 4.—Anomalous blood vessels within the hamartoma. *A*, the abnormally thick intima, the eccentric lumen and the indefinite media and adventitia. *B*, an anomalous artery, showing incomplete, though definite, formation of a media and an abnormally thick intima without any elastica.



popular, but some were pedunculate. In places they were confluent. The nodules were pale red except when she blushed, and then they became bright red and more prominent. They were smooth and somewhat greasy. A few grouped lesions were also seen on her forehead, on the back of her neck below the hair line and in front above the right clavicle.

When the patient and her parents were questioned certain additional facts were learned which made the diagnosis of tuberous sclerosis highly probable. When she was about 4 years old "pimples" had appeared on her forehead and face and had soon reached the extent just described. Since the age of 5 and until one year previously she had had occasional "fainting spells," in which she suddenly grew rigid and fell unconscious. She would recover from these in a

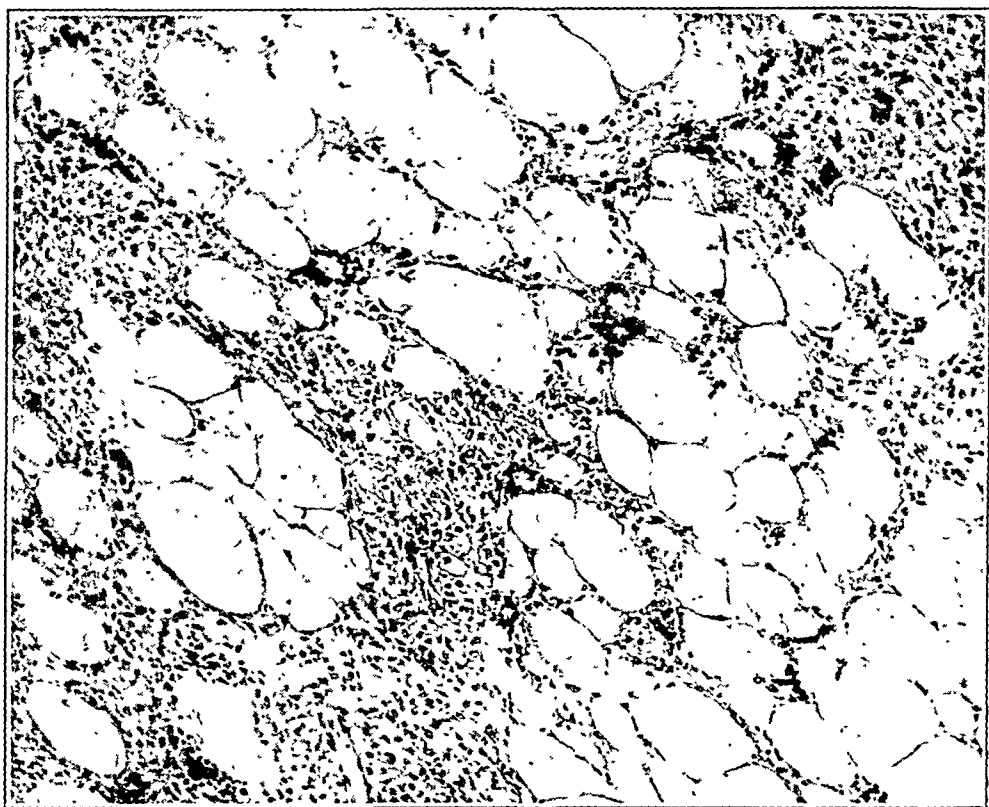


Fig. 5.—Islands of adipose tissue within the hamartoma, showing numerous primitive multinucleated lipoblasts.

few minutes and resume her former activity as if nothing had happened. She had never exhibited violent movements, frothing, tongue biting or incontinence.

She was the eldest of 4 children. The other 3 were apparently entirely well. She had been a normal infant and had begun to talk at the age of 1 year but walked late. She had started to school at the age of 7 and had reached the sixth grade. She was considered slightly backward and had always been "nervous, shy and sensitive." When asked simple questions during the examination she exhibited unusual diffidence. When this was overcome she gave correct answers and showed no gross defect in intelligence.

Her parents were healthy persons of German origin. The family history was lacking in evidence of other instances of the tuberous sclerosis complex, neurofibromatosis or other heredofamilial disorders.



Fig. 6.—Photomicrographs of hamartial “germs” within nontumorous regions of the renal cortex. *A* and *B*, sections containing anomalous cystic tubules lined with cuboidal epithelium of primitive type. *C*, a fibroma-like nodule within the cortex, consisting predominantly of primitive mesenchymal stroma, with few tubules. *D*, the tissue within *C* at a higher magnification.

On a subsequent visit she was examined ophthalmoscopically. The right disk was obscured by a pearly white elliptic plaque with a smooth protuberant surface and a sharp outline. Its long axis was vertical and slightly larger than the diameter of the disk itself. The vessels were covered by this mass.

On Nov. 30, 1937, nearly five years later, she was readmitted to the hospital for treatment of headache and vomiting. She had been perfectly well in the interval. The onset of these disorders had occurred suddenly three days previously, and they had been accompanied on the following day by drooping of the left eyelid and by periodic lapses into mild stupor. Examination showed divergent strabismus of the left eye. There was considerable ptosis of the left upper eyelid (fig. 7 *B*). The left pupil was somewhat dilated and did not react to light. Some pupillary reaction to accommodation and consensual light stimulation was elicited. Slight paresis of the lower part of the face on the left side was also

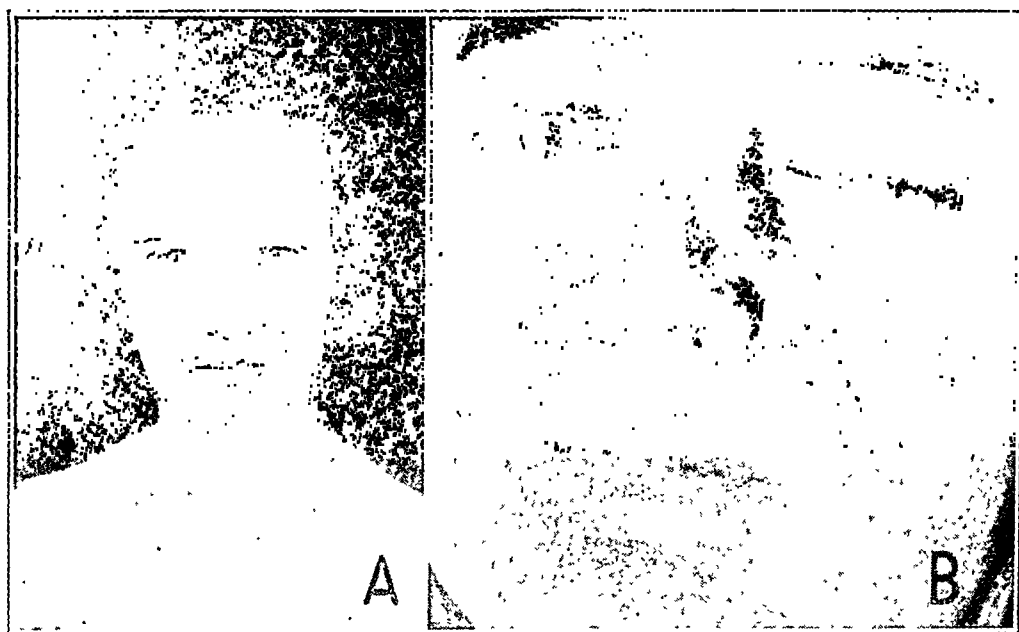


Fig. 7.—*A*, photograph of the patient taken at the age of 15 years, showing adenoma sebaceum. Note the symmetric distribution of lesions on either side of the nose and on the chin, also the scattered lesions on the forehead and neck. *B*, photograph of the patient taken at the age of 20 years, showing a slight increase in the size and extent of the cutaneous lesions, also ptosis and external strabismus of the left eye.

noted. Both fundi exhibited swelling of the nerve head, which was more marked in the left eye. The retinal plaque was much less apparent on the swollen right disk. No other significant neurologic findings were detected. Treatment consisted of dehydrating measures to relieve increased intracranial pressure. During the three weeks of observation in the hospital her condition improved. The neurologic findings varied from time to time in degree, but the headaches and vomiting largely subsided. Periodic drowsiness continued, and the oculomotor changes oscillated from mild to severe. In the opinion of observers the neurologic symptoms were explained by tuberculous foci in the left quadrigeminal body which

encroached on the aqueduct of Sylvius, accounting for the left ophthalmoplegia with Argýll Robertson pupil, the somnolence and the precipitate occurrence of internal hydrocephalus and choked disk. Surgical intervention was considered unwarranted, and the patient was discharged at her own request. She was subsequently admitted to another hospital, where a decompression was performed. She died at home a short time later.

#### PATHOLOGIC AND CLINICAL OBSERVATIONS

*Renal Involvement.*—According to the available data, renal tuberosities affect more than half the persons who have the tuberous sclerosis complex.<sup>6</sup> Because of their small size they are generally latent clinically and are an incidental finding at autopsy. Rarely, however, their bulk and multiplicity are sufficient to cause uremia during the lifetime of the patient. Hemorrhage from the kidney or evidence of suppuration may lead to their discovery ante mortem by means of surgical exploration, as in this case. Pyelography is rarely helpful in their diagnosis because of their size and situation. They may occur in the cortex in the form of multiple discrete nodules of varying size, or they may be agglomerated into a single extensive irregular knobby mass. In some instances part or all of one kidney presents a uniform expansion. Individual nodules are sharply circumscribed and may project prominently above the surface. Their color ranges from grayish white or grayish red to yellowish white or yellow. They may be soft or firm. In addition, they may be combined with one or more gross developmental anomalies of the kidney. In the case reported here the extirpated kidney presented a mushroom-shaped tumor-like overgrowth of its lower third. It was yellowish white and rather firm. Its center was occupied by a large round cavity representing the corresponding, anomalous calix, previously visualized in the pyelogram. An additional, smaller tumor overlay the lower pole. Many anomalous cystic tubules within thickened stroma were seen histologically in sections from other parts of the kidney, which were free of gross abnormality.

Poorly differentiated cells of spindle or myoblast type, as typified in the present case, make up the bulk of these nodules. The cells are fairly uniform and have regular nuclei of medium size and round or oval shape. Despite their primitive aspect, they show no evidence of active proliferation. The intercellular substance is moderate in amount and stains poorly; it suggests a primitive sort of collagen or myoglia. Islands of fat are scattered through the nodules and in some instances comprise the greater part of their substance. Multinucleated steatoblasts may be seen in and around the fully formed fat (fig. 5). The vascular components are well developed and striking. They may predominate, giving the nodule a distinctly angiomatous character. Their structure is neither distinctly arterial nor venous but resembles that of a cirroid aneurysm

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6. Feriz.<sup>2</sup> Kaufmann.<sup>4</sup>

of the brain<sup>7</sup> or a congenital arteriovenous fistula of an extremity.<sup>8</sup> The vessel walls attain great thickness in spite of an extremely small caliber of lumen. Their layers are formed by the concentric apposition of myoblast cells externally like the annual rings of a tree. In some areas almost the entire tissue seems to be composed of ill defined bundles of vasoformative cells. These are without definite order except where they exhibit circular alinement into groups of serpentine thick-walled small or medium-sized blood channels having extremely small lumens (fig. 4). These vessels are notably deficient in elastic tissue<sup>2</sup> and often undergo hyalinization. Other types of tissue, such as epithelium-lined tubules and striated muscle, occur in rudimentary form and in small amount.<sup>2</sup> The cell composition throughout appears slow growing and noninvasive. The atypical cytologic aspects and architecture often suggest neoplasia; hence the terms angiofibroliposarcoma, fibrolipomyo-angioma and fibrolipomyoangiosarcoma applied by some pathologists.<sup>9</sup> A few cases of the tuberous sclerosis complex have been reported in the literature in association with "hypernephroma"<sup>10</sup> or "adenomyosarcoma of Wilms type." It is likely that at least some of these growths belong rightfully with the renal nodules of the tuberous sclerosis complex.<sup>11</sup> When account is taken of their organoid morphology, their limited growth and the underlying nature of the disease as a whole, the renal nodules take on an aspect which compels one to the view now generally held that they are best classified not as neoplasms but as hamartomas.<sup>12</sup>

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7. (a) Cushing, H., and Bailey, P.: *Tumors Arising from the Blood-Vessels of the Brain: Angiomatous Malformations and Hemangioblastomas*, Springfield, Ill., Charles C. Thomas, Publisher, 1928. (b) Levine, V.: *Angiomatous Malformations of the Brain: Report of Two Cases of Angioma Racemosum*, Arch. Path. **15**:340 (March) 1933. (c) Turner, O. A.: *Arteriovenous Hamartoma of the Brain: Report of a Case with Autopsy*, *ibid.* **24**:223 (Aug.) 1937.

8. Blumgart, H. L., and Ernstene, A. C.: *Hemangiectatic Hypertrophy and Congenital Phlebarteriectasis, with Particular Reference to the Diagnostic Importance of the Peripheral Vascular Phenomena*, Arch. Int. Med. **49**:599 (April) 1932.

9. Harbitz, F.: *Tuberöse Hirnsklerose, gleichzeitig mit Nierengeschwülsten (Myxo-Lipo-Sarkomen) und einer Hautkrankheit (Adenoma sebaceum)*, Centralbl. f. allg. Path. u. path. Anat. **23**:868, 1912.

10. In justice to some of the earlier writers on this subject, it should be noted that the term hypernephroma was often used generically for the majority of renal tumors and structures of various types (Ewing,<sup>14</sup> p. 781).

11. (a) Hyman, A.: *The Association of Hypernephroma with Tuberose Brain Sclerosis and Adenoma Sebaceum*, J. Urol. **8**:317 (Oct.) 1922. (b) Yater, W. M.: *Tumors of the Heart and Pericardium*, Arch. Int. Med. **48**:627 (Oct.) 1931.

12. The term hamartoma (Albrecht, E.: *Ueber Hamartome*, Verhandl. d. deutsch. path. Gesellsch. **7**:153, 1904) denotes a tumor-like malformation marked by defects in tissue combination. A well known example is the simple medullary "fibroma" of the kidney. Grossly this is a sharply defined whitish nodule, slightly larger than a pinhead. Microscopically it is a dense aggregate of stromal tissue

True neoplasms in these cases are rare. Only 3 cases of an unmistakable malignant growth (hamartoblastoma) have been reported in which small metastatic deposits were found in other organs (Kirpicznik,<sup>13</sup> Harbitz,<sup>9</sup> Feriz<sup>2</sup>). While it is a fact that areas of perverted cell development are more favorable soil for new growth than are normal tissues,<sup>14</sup> this tendency is so little in evidence in these hamartomas that one is inclined to wonder whether their fetal cell characters do not rather indicate a considerable measure of defectiveness in growth potency. Hamartial "germs" in the form of minute areas of distorted stroma with atypical tubules may be found scattered throughout the otherwise normal parts of the kidney. They may form minute cysts, as in the case reported here.

Isolated hamartomas of the kidney may also occur independently of the tuberous sclerosis complex. The medullary "fibroma" is well known. In addition, solitary lesions of the cortex have been reported under the title benign mixed tumor. They are generally small and are classified by whatever component is predominant, i. e., as hemangioma, lipoma, myoma, fibroma, etc. They are found mostly in adults, and except for infrequent hematuria they are symptomless.<sup>15</sup>

*Cerebral Involvement.*—The cerebral manifestations of the disease are its most constant feature. Moreover, they reveal themselves clinically far more overtly than do the renal or the cardiac lesions. In a majority of the recorded cases the patients were epileptic,<sup>16</sup> and many exhibited

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arranged formlessly and enclosing a few scattered rudimentary tubules; it is poorly defined from the surrounding normal stroma. A wide variety of organoid structures and "benign tumors" are probably also included in the definition. Theoretically, this should include congenital vascular nevi and angiomas, also glomangiomas and cirroid aneurysms and certain types of pigmented and keratotic nevi. There is a growing tendency to regard benign tumors in general not as neoplasms but as hamartomas.<sup>17</sup> The cells of a hamartoma share a common embryonal origin with those of the organ in which they are found. They share to some extent also in the growth of the organ and may later regress.

13. Kirpicznik, J.: Ein Fall von tuberöser Sklerose und gleichzeitigen multiplen Nierengeschwülsten, Inaug. Dissert., Berlin, G. Reimer, 1910; Virchows Arch. f. path. Anat. **202**:358, 1910.

14. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 97.

15. Watson, M. C.: Benign Mixed Tumors of the Kidney, Canad. M. A. J. **18**:511 (May) 1928. MacKenzie, D. W., and Hawthorne, A. B.: Hemangioma of the Kidney: A Report of Two Cases and a Brief Résumé of the Literature, J. Urol. **26**:205 (Aug.) 1931. Bell, E. T.: A Classification of Renal Tumors with Observations on the Frequency of the Various Types, *ibid.* **39**:238 (March) 1938.

16. (a) Hartdegen, A.: Ein Fall von multipler Verhärtung des Grosshirns nebst histologisch eigenartigen harten Geschwülsten der Seitenventrikel ("Glioma gangliocellulare") bei einem Neugeborenen, Arch. f. Psychiat. **11**:117, 1881. (b) Vogt, H.: Die tuberöse Sklerose, Arch. f. Kinderh. **48**:369, 1908. (c) Freeman, W.: Tuberous Sclerosis, Arch. Neurol. & Psychiat. **8**:614 (Dec.) 1922. (d) Footnote 1.

mental retardation and even a severe grade of imbecility. An exceedingly wide variety of epileptic phenomena, psychic and emotional defects and neurologic abnormalities, focal or systematized, have been reported. Diagnosis, however, is rarely established clinically without additional evidence, such as adenoma sebaceum of the skin or phacomia of the retina. Papilledema and other signs of internal hydrocephalus occur infrequently and are traced, as a rule, to expanding lesions in the region of the aqueduct of Sylvius or the third ventricle,<sup>17</sup> such as were diagnosed in the case reported here. In several mature subjects clinical signs of the disease were never noted despite proved lesions in the brain at autopsy.<sup>18</sup> It is rather likely that tuberous foci would be found in every instance of the complex in which autopsy was done, including the "forme fruste," if the brain was examined with sufficient care (Feriz<sup>2</sup>). Instances of the disease in infancy have also been recorded.<sup>19</sup> In general, however, there is a delay of several years after birth before the appearance of epilepsy and the other clinical aspects of the disease.<sup>20</sup> A survey of the subject, with an excellent discussion of its clinical neurology, may be found in the paper of Critchley and Earl (1932).<sup>18a</sup>

The morphologic manifestations of the disease in its cerebral localization are variable.<sup>21</sup> The surfaces of the cerebral hemispheres are found to be the seat of areas of peculiar hardening, white or mottled with gray and scattered irregularly. These areas are of varying size and may be nodular and circumscribed but are often indefinite in outline. In addition, entire convolutions or groups of convolutions may be deformed, either narrowed (microgyria) or widened (macrogyria). On section the transition from gray to white matter is indistinct or completely lost in these regions. In over half the cases irregular projections

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17. (a) Globus, J. H.; Strauss, I., and Selinsky, H.: Das Neurospongioblastom, eine primäre Gehirngeschwulst bei disseminierter Neurospongioblastose (tuberöse Sklerose), *Ztschr. f. d. ges. Neurol. u. Psychiat.* **140**:1, 1932. (b) Globus, J. H.: Neurinome central associé à une sclérose tubéreuse (neurospongioblastose disséminée), *Rev. neurol.* **2**:1 (July) 1933. (c) Stevenson, L. D., and McGowan, L. E.: A Case of Tuberous Sclerosis Involving Chiefly the Cerebellum and Simulating an Expanding Lesion of the Quadrigeminal Plate, *Tr. Am. Neurol. A.* **63**:26, 1937. (d) Liber, A. F.: Tuberous Sclerosis with Cerebellar Involvement and a Colloid Cyst of the Septum Pellucidum, *Arch. Path.* **26**:753 (Sept.) 1938.

18. (a) Critchley, M., and Earl, C. J. C.: Tuberous Sclerosis and Allied Conditions, *Brain* **55**:311 (Sept.) 1932. (b) Feriz.<sup>2</sup>

19. Globus, J. H., and Selinsky, H.: Tuberous Sclerosis in the Infant, *Am. J. Dis. Child.* **50**:954 (Oct.) 1935.

20. Yakovlev, P. I.: Congenital Morphologic Abnormalities of the Brain in a Case of Abortive Tuberous Sclerosis: Functional Implications and Bearing on Pathogenesis of So-Called Genuine Epilepsy, *Arch. Neurol. & Psychiat.* **41**:119 (Jan.) 1939.

21. Kaufmann,<sup>4</sup> vol. 2, p. 1479.

occur on the inner surface of the lateral ventricles. These have often been described as resembling candle gutterings. They may be confluent, however, and may form a dense sclerotic layer. Rarely they take the form of large projecting intraventricular tumors. The cerebellum and spinal cord are rarely affected.

Histologically a variety of cell types is found; these are unique in their unusual configuration and in their frequently gigantic size. Despite their malformed appearance, many intermediate types can be traced between finely branched primitive neuroglial cells (spongioblasts) and gigantic structures of ganglion cell type (neuroblasts) with a large nucleus. The glial elements predominate to a marked degree. Probably all these abnormal cells are collateral derivatives of primordial undifferentiated neuroepithelium (Globus and associates<sup>22</sup>).

An essential feature of the cerebral lesions is the evidence of failure of cell migration during embryonal development. The loss of cortico-medullary demarcation in the affected gyri, visible grossly, corresponds histologically with an appearance of "profound confusion of the cortical cytoarchitecture" (Yakovlev<sup>20</sup>). The vascular architecture is similarly deformed, so that a poverty of circulation exists in the affected cortex together with a surplus of vessels in the corresponding subcortical white matter.<sup>20</sup> The blood vessels have thickened walls, somewhat like those in the renal nodules, and calcific deposits occur frequently in and around them.

Transitions are frequently found from diffuse gliosis to focal circumscribed glioma-like overgrowths.<sup>23</sup> Although the multiple foci in the brain are undoubtedly hamartial in nature, true neoplasia is nevertheless a not infrequent occurrence. The tumors are often multiple. Histologically they differ from ordinary gliomatous growths in exhibiting traces of ganglion cell elements, so that they represent actually a form of mixed tumor of the brain (neurospongioblastoma, Globus and associates<sup>24</sup>). The relation between neoplasia and the benign hamartial "germs" and thickenings is one of the most interesting aspects of the disease.

*Relation Between Tuberous Sclerosis and Brain Tumor.*—The case for a heightened incidence of neoplasm in tuberous sclerosis of the brain seems fairly well established as a result of the studies of Biel-

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22. (a) Globus, J. H.: Primary Neuroectodermal Brain Tumors: Their Transition from Benign to Malignant Forms, *J. Mt. Sinai Hosp.* **7**:361 (Jan.-Feb.) 1941. (b) Footnote 17 *a* and *b*.

23. (a) Bielschowsky, M.: Zur Histopathologie und Pathogenese der tuberösen Sklerose, *J. f. Psychol. u. Neurol.* **30**:167, 1924. (b) Kaufmann.<sup>21</sup>

24. Globus, J. H.: Glioneuroma and Spongioneuroblastoma, Forms of Primary Neuroectodermal Tumors of the Brain, *Am. J. Cancer* **32**:163 (Feb.) 1938; footnote 22.



schowsky,<sup>23a</sup> Globus and associates<sup>25</sup> and other authorities.<sup>26</sup> Bielschowsky expressed a preference for the view that the disease is the result of a widespread and disseminated blastomatous agency which is active in early embryonic life. On this basis he explained not only the primitive and multifarious cell components of the nodules in the brain and other affected organs but the disorder in architecture resulting from failure of normal cell migration. Pellizzi (1901)<sup>27</sup> and subsequent writers<sup>28</sup> have, for the most part, expressed opinions that the essential lesions of the disease itself represent the product of retardation in cell differentiation and migration, hence a form of disseminated congenital malformation (hamartiosis). The foci of sclerosis and of nodular overgrowth of the brain are accordingly viewed as homologous with the hamartomas in the skin, heart and kidneys. Since the weight of evidence is opposed to the view that the latter manifestations of the disease are neoplastic, it is unlikely, therefore, that the cerebral foci are intrinsically neoplastic. Globus<sup>22a</sup> directed attention to the possibility of the transition of growths in the brain from benign to malignant, in accordance with the Cohnheim-Ribbert theory of origin of neoplasms in embryonal rests. If the term embryonal rest is merely restated as hamartial malformation the entire concept of transition of a neoplasm from benign to malignant is simplified. In effect, the basic lesion is hamartial, becoming in turn tumor-like but benign (hamartoma) and truly neoplastic (hamartoblastoma, viz., neurospongioblastoma).

Certain types of evidence will be cited later which enable one to make a special case for the high incidence of cerebral neoplasm in tuberous sclerosis without doing violence to the concept that the underlying basis for the disease is a disseminated tissue malformation (hamartiosis). Briefly stated, defective organization in the embryonic brain is carried into mature existence in the form of unrealized cell potencies for differentiation and of refractoriness to local and neurotrophic organizer influences. These foci are thereby neither integrated in function nor protected against individualistic tendencies in the cells to proliferate and to form tumors. As a result, they constitute a constant latent source of neoplasia in which cell activation may occur at any time in one or more places. This will be referred to again in connection with the etiology of the disease.

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25. Footnote 17 *a* and *b*.

26. Ferraro, A., and Doolittle, G. J.: Tuberous Sclerosis (Diffuse Neurospongioblastosis), *Psychiatric Quart.* **10**:365 (July) 1936.

27. Pellizzi, cited by Ferraro and Doolittle.<sup>26</sup>

28. (a) Yakovlev, P. I., and Guthrie, R. H.: Congenital Ectodermoses (Neurocutaneous Syndromes) in Epileptic Patients, *Arch. Neurol. & Psychiat.* **26**:1145 (Dec.) 1931. (b) Feriz.<sup>2</sup> (c) Kirpicznik.<sup>13</sup> (d) Footnote 17 *a* and *b*. (e) Critchley and Earl.<sup>18a</sup>

*Cutaneous Lesions.*—Lesions of the skin when present are of pre-eminent importance in the clinical recognition of the disease. Their best known form, adenoma sebaceum, is seen in about half the cases.<sup>5</sup> Its appearance on the face is striking and pathognomonic. Properly the condition should be designated hamartoma pilosebaceum, having the same background of faulty development as the tuberous lesions in the brain or kidney. It takes the form of closely grouped nodules, with a butterfly distribution along the nasolabial folds on both cheeks, converging below to the chin (fig. 7). The nodules are most numerous on either side of the nose. They are easily distinguished from the lesions of acne, including that caused by prolonged ingestion of a bromide. Scattered nodules also occur on the forehead and neck. The individual lesions are wartlike or papular and yellow or red. In the case reported here they became bright red whenever the patient blushed. In this as in several other reported cases an angiomaticous component was apparently prominent (Pringle type<sup>29</sup>). Peculiar changes in the texture and pigmentation of the skin are often noted in isolated areas in other parts of the body.<sup>30</sup> These, too, have diagnostic significance.

*Cardiac Involvement.*—The so-called "rhabdomyoma" of the heart has been reported in about half the cases in which typical cerebral changes were exhibited.<sup>31</sup> Thorough examination might possibly have disclosed less obvious defects of tissue structure in the heart in nearly every case (Feriz<sup>2</sup>). Conversely, in only half the recorded cases of rhabdomyoma cordis is associated cerebral disease reported (Cagnetto<sup>3b</sup>), despite evidences of the complex in other organs (kidneys, skin, retina). Here, too, the suspicion exists that complete study of the brain with serial sections would have brought to light the typical pattern of cerebral changes.<sup>2</sup> It is probable, however, that this may be said with assurance only of diffuse or multiple rhabdomyomatosis of the heart, whereas a solitary rhabdomyoma may occur either as part of the complex or as an independent lesion (Mönckeberg<sup>31b</sup>).

In the heart, as in other affected organs, the nodules and swellings are now regarded as tissue malformations (hamartomas) and not as neoplasms.<sup>32</sup> The component cells have an appearance suggesting

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29. Pringle, J. J.: Ueber einem Fall von kongenitalen Adenoma sebaceum, *Monatsh. f. prakt. Dermat.* **10**:197, 1890.

30. (a) Urbach, E., and Wiedmann, A.: Morbus Pringle und Morbus Recklinghausen: Ihre Beziehungen zueinander, *Arch. f. Dermat. u. Syph.* **158**:334, 1929. (b) Pringle.<sup>29</sup> (c) Feriz.<sup>2</sup> (d) Footnote 5.

31. (a) Yater.<sup>11b</sup> (b) Mönckeberg, J. G.: Rhabdomyom des Herzens, in *Geschwülste und Parasiten des Myokards und des spezifischen Muskelsystems*, in Henke, F., and Lubarsch, O.: *Herz und Gefässe*, in *Handbuch der speziellen-pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1924, vol. 2, p. 482.

32. (a) Bonome, cited by Mönckeberg.<sup>31b</sup> (b) Farber, S.: Congenital Rhabdomyoma of the Heart, *Am. J. Path.* **7**:105 (March) 1931. (c) Rehder.<sup>3a</sup> (d) Mönckeberg.<sup>31b</sup>

embryonal heart fibers, but they are often remarkably misshapen and enlarged to grotesque proportions. Numerous scattered "germs" of embryonal heart muscle are often discovered microscopically in areas which are grossly normal.<sup>31b</sup> No tendency to autonomous growth is evident, and the picture here, like that in the brain and kidneys, is apparently that of a "concluded process" (Kirpicznik<sup>13</sup>). The morphologic nature of these structures remains fixed throughout the subject's lifetime except for fibrous replacement or calcification.<sup>31b</sup> Large nodules may cause obstruction of an important channel, such as the trunk of the pulmonary artery,<sup>33</sup> and cause death through heart failure at an early age. In many cases, however, despite considerable involvement, little or no interference with cardiac function occurs.

Painstaking search often reveals many homologous, though less obvious, changes in other parts of the vascular apparatus. Here, too, the aspect is that of a flaw in development. Ill defined thickenings appear in the walls of certain blood vessels, and their myoelastic architecture shows various degrees of imperfection.<sup>34</sup> Certain types of angioma possibly fall into this category as well. In addition, the hamartomas of the kidneys, skin or brain may contain a large angiomatous component.

*Retinal Lesions (Syndrome of van der Hoeve<sup>35</sup>).*—Tumor-like lesions of the retina have been observed in a number of cases of the tuberous sclerosis complex during life. Like the nodules in the skin they are pathognomonic of the disease. They have usually been found separate from the disk but occasionally occur on the disk itself, as in the case reported here. Their ophthalmoscopic appearance is that of white or gray areas which are round or elliptic. They may be large and appreciably elevated or small and appearing only as flat plaques. They may be smooth or mulberry-like in contour and are sometimes cystic.<sup>36</sup> The term phacoma has been applied to them. Structurally they are hamartomas of predominantly gliogenous nature, containing possibly a few undifferentiated ganglion cells.<sup>37</sup> It is probable that their determination in the primitive optic neuroepithelium takes place from the fourth to the fifth week of embryonic life (Mann<sup>38</sup>).

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33. Wolbach, S. B.: Congenital Rhabdomyoma of the Heart, J. M. Research **11**:495, 1907. Rehder.<sup>3a</sup> Footnote 32 *a* and *b*. Feriz.<sup>2</sup>

34. Böhm, cited by Feriz.<sup>2</sup>

35. van der Hoeve, J.: Augengeschwülste bei der tuberösen Hirnsklerose (Bourneville), Arch. f. Ophth. (a) **105**:880, 1921; (b) **111**:1, 1923.

36. Tarlau, M., and McGrath, H.: Pathologic Changes in the Fundus Oculi in Tuberous Sclerosis: Clinical and Pathological Report of a Case of Tumor Arising from the Optic Nerve Head with a Review of the Literature, J. Nerv. & Ment. Dis. **92**:22 (July) 1940.

37. Messinger, H. C., and Clarke, B. E.: Retinal Tumors in Tuberous Sclerosis, Arch. Ophth. **18**:1 (July) 1937.

38. Mann, I.: Personal communication to Messinger and Clarke.<sup>37</sup>

*Osseous Lesions.*—A case of this disease was reported<sup>39</sup> in 1935 in which roentgenograms of the skull revealed numerous indistinct islands of increased density alternating with areas of rarefaction, together with increased thickness and density of the tables of the skull. Comparable changes were also noted in the bones of the hands and feet. The remainder of the skeleton was free of roentgenologic abnormalities except for spina bifida. Since then, other cases of tuberous sclerosis have been reported in which similar observations were made.<sup>40</sup> In addition, a case has been reported<sup>40b</sup> in which roentgenograms revealed peculiar “flowing” hyperostoses along the shafts of certain bones, typical of the condition known as melorheostosis (Léri). The similarities of the bone changes in tuberous sclerosis to those in multiple neurofibromatosis have been pointed out by certain writers and ascribed either to an overlapping of the two syndromes or to a dysontogenetic factor possessed by both in common.

*Coexisting Anomalies of Development.*—In several of the reported cases important gross developmental defects were found. These included cyst of the septum pellucidum,<sup>17d</sup> spina bifida,<sup>41</sup> cleft palate,<sup>42</sup> accessory lung,<sup>43</sup> malformation of the pancreas,<sup>44</sup> fused kidney with dystopia cruciata,<sup>2</sup> cardiac defects,<sup>45</sup> subaortic stenosis,<sup>18a</sup> subnormal development of the arch of the aorta<sup>27</sup> and congenital ramifying diverticulum of the left ventricle of the heart.<sup>46</sup> Minor developmental anomalies, however, occur in nearly all the cases,<sup>2</sup> as well as so-called “stigmas of degeneracy.”<sup>47</sup> From the standpoint of the pathogenesis of the syndrome, these defects are probably nonspecific yet cannot be considered unrelated. Their significance is best understood when discussed in connection with the pathogenesis of the disease.

#### ETIOLOGY AND PATHOGENESIS

*Theories.*—Whatever the nature of its pathogenetic mechanism, the disease is clearly inherent in the germ plasm before conception takes

39. Gottlieb, J. S., and Lavine, G. R.: Tuberous Sclerosis with Unusual Lesions of the Bones, *Arch. Neurol. & Psychiat.* **33**:379 (Feb.) 1935.

40. (a) Dalsgaard-Nielsen, T., cited by Hall. (b) Hall, G. S.: Tuberose Sclerosis, Rheostosis and Neurofibromatosis, *Quart. J. Med.* **9**:1 (Jan.) 1940.

41. Hartdegen.<sup>16a</sup> Gottlieb and Lavine.<sup>39</sup>

42. Jonas, W.: Zur Histologie der tuberösen Hirnsklerose an der Hand eines durch Rhabdomyome des Herzens komplizierten Falles, Frankfurt. *Ztschr. f. Path.* **11**:105, 1912.

43. Kirsch-Hertel, cited by Feriz.<sup>2</sup>

44. Kawamura, R., cited by Farber.<sup>32b</sup>

45. Adrian, C.: Ueber Neurofibromatose und ihre Komplikationen, *Beitr. z. klin. Chir.* **31**:1, 1901. Bourneville and Brissaud.<sup>1b</sup> Berdez, cited by Feriz.<sup>2</sup>

46. Norman, R. M., and Taylor, A. L.: Congenital Diverticulum of Left Ventricle of Heart in Case of Epiloia, *J. Path. & Bact.* **50**:61 (Jan.) 1940.

47. Kirpiczink.<sup>13</sup> Critchley and Earl.<sup>18a</sup>

place. It is transmitted generally in accordance with well defined heredo-familial patterns. According to Penrose,<sup>48</sup> its genetic behavior is that of a mendelian dominant. In addition, the disease crops out sporadically in apparently healthy stock, as in the case reported here. Such occurrences are regarded as the result of mutation.

Further analysis of its etiology lies in the realm of hypothesis. According to older views, especially that of Bielschowsky,<sup>23a</sup> the disease is the manifestation of a neoplastic agency active in early embryonal life. On the other hand, the remarkable fidelity to pattern with which the disease reproduces itself in different organs and in different persons, the parallel development of its widely separate lesions, their organoid structure and the relative conformity of their rate of growth and retrogression with that of the host tissues militate strongly against this point of view.

Yakovlev and Guthrie<sup>28a</sup> attempted recently to establish the concept that tuberous sclerosis, like neurofibromatosis and certain other syndromes, is a system disease of neuroectodermal structures (ectoblast). These writers pointed to the simultaneous occurrence of cerebral lesions with adenoma sebaceum of the skin in the first-named condition and of peripheral nerve tumors with cutaneous nevi and, occasionally, adenoma sebaceum in the second one, also to several instances of apparent overlapping between the two syndromes. They explained the occurrence of angiomas and of hamartomas of the kidneys and heart, which are derived from mesodermal elements, as trophic formations determined by abnormalities of the sympathetic nerves. Their evidence is ingenious but not entirely convincing. The visceral lesions of tuberous sclerosis in the heart and kidneys are homologous in every way with the lesions of the skin and brain.

The element of heredity plays a determining role so frequently in the occurrence of the tuberous sclerosis complex that the disease must be regarded basically as the outcome of a genic abnormality within the germinal elements of the affected individual. Theoretically, the determiners of the disease may be assumed to enter into and to disturb the embryonal pattern in several widely separated regions at a selectively predetermined stage of development which is identical in all cases. Some estimates place the time of this disturbance between the third and fourth months of intrauterine life, but there is much authority for placing it earlier.<sup>49</sup> If inferences are drawn from the structure of the lesions themselves, the timing of this event should coincide with a stage of tissue ambivalence in which differentiation has not yet progressed far but in which various organs have already become defined. Among these

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48. Penrose, L. S.: *The Influence of Heredity on Disease*: Buckston Brown Prize Essay, 1933, London, H. K. Lewis & Co., 1934, p. 61.

49. Feriz.<sup>2</sup> Kirpicznik.<sup>13</sup> Mann.<sup>38</sup>

must necessarily be included the metanephros, or future kidney, of which no vestige exists until the fifth week, when the ureteric evagination first appears. Since the renal hamartomas are composed chiefly of derivatives of primitive nephrogenic mesenchyme, it is likely that they owe their inception to a disturbance affecting the organization of the latter about the ends of the primordial collecting tubules. This point of differentiation is not reached normally until about the sixth week.

The frequent occurrence of unrelated developmental anomalies (accessory lung, spina bifida, fused kidney, etc.) gives some basis for the suggestion that the determination of the tuberous sclerosis complex may even begin to take place somewhat prematurely, so that organ differentiation is disturbed as well as cell differentiation (Feriz<sup>2</sup>).

*The Role of Embryonic Organizers and Cell Competence in Normal Differentiation and in Malformation.*—The pathogenesis of the tuberous sclerosis complex, like that of any developmental anomaly, may be stated to depend, generally speaking, on faulty differentiation of embryonic cells at critical points of development. Cell migration and organ construction are thereby impeded or wholly frustrated; proliferation, however, may not be greatly affected and may even be accelerated. Spemann<sup>50</sup> and others<sup>51</sup> have provided important clues to an understanding of the principles involved in faulty differentiation. In their studies on embryonic development they have shown that differentiation depends on two major factors, an intrinsic predisposition within cells to undergo specialization ("cell competence") and an inductive stimulus of chemical nature elaborated by certain previously specialized cells ("organizers"). The two factors are anatomically and functionally related. The primitive lens, for instance, is formed by differentiation of ectodermal cells in the head region in response to the inductive stimulus of the outgrowing optic vesicle of the forebrain. Ectodermal cells from other regions may also undergo lens differentiation if transplanted to the head region overlying the optic vesicle; conversely, transplantation of the optic vesicle will induce lens formation beneath the ectoderm of any region. The optic vesicle is said to be an "organizer" for lens formation. On the other hand, ectoderm normally intended for lens formation may be induced to undergo this change in the absence of the optic vesicle itself when subjected to the action of soluble substances extracted from the cells of the latter. According to Needham,<sup>51</sup> such substances are of definite chemical structure, being sterols homologous with estrogen and certain carcinogenic hydrocarbons. This is disputed by Spemann, who induced differentiation by extracts from many other parts of the

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50. Spemann, H.: *Embryonic Development and Induction*, Silliman Memorial Lectures, New Haven, Conn., Yale University Press, 1938.

51. Needham, J.: *New Advances in the Chemistry and Biology of Organized Growth*, Proc. Roy. Soc. Med. **29**:1577 (Oct.) 1936.

embryo and even by simple acids (oleic acid, linoleic acid, nucleic acids and adenylic acid) but not by the ether-soluble nonhydrolyzable sterol fractions. The exact role of these acids is not clear, and they may serve merely as activators of some of the aforementioned sterols.

The harmonious interplay of these two factors, cell competence and organizer induction, insures complete integration between component cells of each growing organ. It seems likely that this principle of "double assurance" governs the growth of all embryonal structures. In other words, organizer influences depend not only on their own relative potency but on cell competence as well. The latter becomes less as differentiation approaches completion, and the fully differentiated cell may be said to be relatively refractory to organizer influence. Up to a certain stage of growth, however, a considerable measure of reversibility exists. Mesodermal tissue which has become notochord is capable of inducing the formation of a secondary neural plate in any part of the epidermis. Ectoderm may even become converted to notochordal mesoderm if transplanted into a powerful organizing "field," such as the region of the foregut; this mesoderm, in turn, becomes capable of inducing neural differentiation in any undifferentiated ectoderm. Entoderm, on the other hand, possesses an astonishing power of self-differentiation, in contrast to the high degree of induction susceptibility of ectoderm. The inductive power of mesoderm extends over a long period of development, far beyond the stage in which induction normally comes into play.<sup>50</sup> The theory of the immutability of the three germ layers is thus clearly superseded by the newer doctrine of differentiation by multiple organizers.

Transplantation of cells of the dorsal lip of the primordial blastopore induces the formation of an entire secondary, parasitic embryo in any portion of the host embryo. This capacity is to a lesser degree inherent in any part of the embryo, probably even in every cell, but its realization is suppressed by previously established organizers.<sup>52</sup> Injurious factors, such as heat, dryness and overripeness of the egg before fertilization, have been shown (in the frog) to interfere with the development of a normal hierarchy of organizers. In the chick similar effects have been produced by subjecting eggs to a subnormal temperature (90 F.) for the first forty-eight hours or more of incubation.<sup>53</sup> As a result, multiple competing organizers are released for simultaneous action on cellular substrates, and multiple malformations ensue (Witschi<sup>54</sup>).

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52. Witschi, E.: Appearance of Accessory "Organizers" in Overripe Eggs of the Frog, *Proc. Soc. Exper. Biol. & Med.* **31**:419 (Jan.) 1934.

53. Smith, L. E. W.: Effect of Temperature on the Development of the Chick Embryo, *Arch. Path.* **28**:422 (Sept.) 1939.

54. Witschi, E.: (a) Experimentally Produced Neoplasms in the Frog, *Proc. Soc. Exper. Biol. & Med.* **27**:475 (March) 1930; (b) footnote 52.

By interference with the orderly sequence of embryonic organizers or by alteration of the spatial configuration of various induction centers, numerous malformations, such as ectopias and duplications (plus formations) have been produced experimentally. In addition, embryonal defects of many sorts have been seen in which the mechanism seems to have been a partial or complete suppression of embryonic induction (minus formations). Lehmann<sup>55</sup> found that the administration of chlorobutanol abolished specifically the induction of the lens by the optic vesicle and resulted in complete suppression of the lens or formation of an abnormally small lens. Lens formation was also blocked by the interception of a thin layer of mesodermal cells between the epidermis and the optic vesicle.<sup>56</sup> Lithium salts were found to inhibit the development of the embryonic notochord.<sup>51</sup> Hale described eyeless pigs born of vitamin A-deficient sows, and in similar experiments Zilva, Goldring, Drummond and Coward reported failure of limb formation. These and other examples prove that faulty differentiation occurs either through a diminution in cell competence in spite of normal inductive stimulus or through interference with the mechanism of organizer induction in normal cells. The operation of the principle of "double assurance" makes it probable that minor degrees of insufficiency of either factor do not interfere with differentiation.

*Organizer Principles in Postembryonic Life and Their Bearing on the Tumor Problem.*—Growth and individuation of cells do not come to an end with the birth of the individual. Regeneration of tissue after injury and to offset wear and tear involves not only a proliferation of "competent" reserve cells, usually only partly differentiated, but their maturation and architectural conformity in the preexisting "organization field." It is a fair assumption, then, that differentiation by organizer induction in the embryo represents only the initial phase of a biologic mechanism governing cell integration in the whole organism throughout life.

Little more than supposition can be made now in regard to the nature and situation of organizers within any given organ. They may be assumed to reside within certain of its cells, possibly in certain interstitial cells of the stroma (cf. the inductive power of mesoderm in the embryo), acting in the manner of an intrinsic hormone for the organ. Since the term organizer has nothing specific in its connotation, there is no reason to exclude from this concept the organizing action of certain extrinsic substances which govern cell differentiation in single organs, in physiologic groups of organs or in the body as a whole. In this broader view of organizers may therefore be included the definitive

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55. Lehmann, cited by Spemann.<sup>50</sup>

56. Deleted by author.



endocrine organs of the body and possibly certain dietary factors. Taking an example at random, one may regard the genesis and entire life cycle of the corpus luteum as an organizer effect of certain hypophysial factors on the ovarian follicle. In a similar light one may regard the influence of vitamin C on the differentiation of mesenchymal cells into osteoblasts.<sup>57</sup> The term organizer as applied within the meaning of this paragraph actually refers to a category of substances, intrinsic or extrinsic to a given organ and known or unknown, which possess in common a hormone-like action on immature cells to induce their specific differentiation.

**Organizers and Tumors:** Investigators have not been laggard in attempting to draw comparisons between cell behavior of embryos and that of tumors. The newer work on embryonic organizers has therefore attracted increasing interest on the part of students of the tumor problem. At present, however, only certain suppositions may be hazarded, and these may soon be superseded as new facts come to light.

The present study of the pathogenesis of the tuberous sclerosis complex brings into the foreground the question of the organizer field as it concerns both abnormal development and malignancy. That the two are in some way related has long been suspected, and the dysontogenetic origin of certain cancers has been clearly established. The cancer cell may be described generally as the product of faulty differentiation of a proliferating cell, arising from reserve cells in the course of tissue regeneration. According to one view, the normal competence of such cells (i. e., their intrinsic genetic predisposition to complete their differentiation) becomes weakened by "carcinogenic" factors, chemical, physical, hormonal or infectious, so that these cells become refractory to organizer influences and may continue to proliferate excessively and eventually without limit. It has been suggested, therefore, that cancerization represents a true mutation. In addition, evidence has been accumulated to show that such anaplastic cells, potentially ancestral to cancer, are formed rather frequently (Fischer<sup>58</sup>), but for the most part remain latent, undergo delayed differentiation or die, so that actual cancers arise in only certain members of the population and usually rather late in life. So great is the diversity among individuals and species in susceptibility to cancer that investigators have turned their attention more and more from the cancer cell to the cancer host.

The principle of the organizer field, applied to problems of carcinogenesis, is concerned primarily with the state of the tissue in which cancer develops. Marked variations in "resistance" to neoplasm are

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57. McLean, D. L.; Sheppard, M., and McHenry, E. W.: Tissue Changes in Ascorbic Acid Deficient Guinea-Pigs, *Brit. J. Exper. Path.* **20**:451 (Dec.) 1939.

58. Fischer, A.: The Theory of the Developmental Physiology of Malignant Tumors, *Am. J. Cancer* **31**:1 (Sept.) 1937.

encountered in man and in lower animals,<sup>59</sup> and susceptibility to spontaneous or induced neoplasm in animals may be markedly raised or lowered by a number of experimental procedures.<sup>60</sup> As previously stated, organizer effects are in a broad sense hormonal but are local or general in their origin and effect and may be transient or permanent. Since their nature is far too vague at present for any attempt at definite characterization, they are best understood, perhaps, by inference from conditions in which, presumably, their action is impaired. The following general factors may be concerned: (a) the stroma of tissues, (b) the age of the organism, (c) the functional state of the nerve supply of the tissues and (d) preexisting anomalies of development.

(a) The stromal factor in malignancy. The possibility was mentioned previously that the site of organizer production in mature organs may be the cellular constituents of their stroma. It should be recalled that the inductive power of embryonic mesoderm has been shown to extend over a long period of development, and its continuation in post-embryonic life may therefore be reasonably sought in such mesodermal derivatives as the stroma of organs, the spleen and various types of connective tissue. Morton and Beers (1935<sup>61</sup>) reported the demonstration in normal human connective tissue of a tumor growth-inhibiting factor. Baker,<sup>62</sup> moreover, attempted to retard the progress of cancer in

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59. Warren, S., and Gates, O.: Spontaneous and Induced Tumors of the Guinea Pig, *Cancer Research* **1**:65 (Jan.) 1941.

60. (a) Mori, K., and Nakahara, W.: Effect of Liver Feeding on the Production of Malignant Tumors by Injections of Carcinogenic Substances, *Gann* **34**:48 (April) 1940; abstracted, *Cancer Research* **1**:77 (Jan.) 1941. (b) Sugiura, K., and Rhoads, C. P.: Experimental Liver Cancer in Rats and Its Inhibition by Rice-Bran Extract, Yeast, and Yeast Extract, *ibid.* **1**:3 (Jan.) 1941. (c) Gross, L.: Experimental Anti-Cancerous Immunity, *J. Mt. Sinai Hosp.* **6**:146 (Sept.-Oct.) 1939. (d) MacFadyen, D. A.; Sturm, E., and Murphy, J. B.: Inhibition of Transplantable Mouse Tumor Growths by Tissue Extracts and Their Protein Fractions, *J. Exper. Med.* **70**:475 (Nov.) 1939. (e) Maisin, J., and Pourbaix, Y.: Growth-Promoting and Growth-Inhibiting Substances from Normal Organs, *Am. J. Cancer* **24**:357 (June) 1935. (f) Lewisohn, R.; Leuchtenberger, R., and Laszlo, D.: Spleen Extract in the Treatment of Transplanted and Spontaneous Malignant Tumors in Mice, *Surg., Gynec. & Obst.* **71**:274 (Sept.) 1940. (g) Cheever, F. S., and Janeway, C. A.: Immunity Induced Against the Brown-Pearce Carcinoma, *Cancer Research* **1**:23 (Jan.) 1941. (h) Russell, B. R. G.: The Nature of Resistance to the Inoculation of Cancer, *Scient. Rep. Invest. Imp. Cancer Research Fund* **3**:341, 1908. (i) Salter, W. T.; Nathanson, I. T., and Wilson, H.: Experimentally Induced Benignancy of Neoplasm: V. The Influence of Hormones on the Host's Resistance to Implanted Neoplasm, *Cancer Research* **1**:60 (Jan.) 1941.

61. Morton, J. J., and Beers, D. N.: The Demonstration of a Tumor Growth-Inhibiting Factor from Normal Human Connective Tissue, *J. Exper. Med.* **61**:59 (Jan.) 1935.

62. Baker, H. S.: The Treatment of Cancer with Connective Tissue Extracts, *Lancet* **2**:643 (Sept. 16) 1933.

human patients with connective tissue extracts and reported a certain measure of success. The recent work of Lewisohn and his co-workers<sup>60f</sup> on the use of spleen extracts in tumor-bearing animals arouses interest in the spleen as a factor of particular importance to the organism as a whole as a specialized source of the same (or similar) organizer principles as found in the embryonal mesoderm.

Indirect evidence of the relation of the organizer principle to the stroma of organs is obtained from pathologic observations which indicate a decided predisposition to malignancy in tissues which have undergone marked fibrosis. The best known examples are seen in instances of carcinoma of the breast occurring in fibrous mastopathies, carcinoma of the liver in cirrhosis and carcinoma of the skin in ancient scars of cutaneous burns. Since the nature of the organizer within mature organs is practically unknown, it is impossible to formulate any definite idea of the mechanism by which its effect is frustrated in the presence of marked stromal fibrosis. It would be interesting, none the less, to compare the tumor-inhibiting action of extracts of normal organs with those of organs in which the stroma has become replaced by indifferent scar tissue.

(b) The age factor. Aging is another factor predisposing to malignancy. In the later decades of life, organizer activity may be said *a priori* to have begun to wane along with other tissue functions and even cells of a relatively low order of anaplasia are liberated from restraining influences. For the same reason, numerous hamartoma-like changes also take place, such as the development of hyperkeratoses, soft fibromas and capillary angiomas of the skin, also benign adenomatous polypi and papillomas of mucous membranes. In the embryo, in infancy and in childhood, on the other hand, organizer activity may be presumed to be of such potency that only under certain special conditions do tumors succeed in gaining headway at all. Malignant tumors in infants and children are of embryonal type, often of complex teratoid structure, and are probably of dysontogenetic origin in the great majority of cases, even though they may not appear until some years after birth.<sup>63</sup> They progress rapidly and metastasize widely. Lymphocytic reaction and hyalinization of stroma are absent to a notable degree.<sup>63</sup> Certain instances have been recorded in human infants in which highly malignant tumors (neuroblastomas) have undergone spontaneous regression, with either complete cure or partial remission into a much more benign type of growth.<sup>64</sup> It is an inviting thought that in young individuals organizer influences appear to be sufficiently powerful to succeed at times in regaining dominance over the cells of a vigorous malignant growth. The potency of

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63. Dargeon, H. W.: *Cancer in Childhood, and a Discussion of Certain Benign Tumors*, St. Louis, C. V. Mosby Company, 1940, pp. 17-18.

64. Wells, H. G.: Occurrence and Significance of Congenital Malignant Neoplasms, *Arch. Path.* **30**:535 (Aug.) 1940.

organizers in youth probably also explains the delay in clinical appearance of such hereditary or familial hamartomatous diseases as adenomatosis of the colon<sup>65</sup> and multiple neurofibromatosis,<sup>66</sup> as well as the tuberous sclerosis complex.<sup>20</sup> Several years often elapse before the earliest manifestations of these disorders appear, although they are undoubtedly determined in the tissues long before birth.

The possibility of influencing favorably the resistance to malignancy of tumor-bearing animals by treatment with embryo emulsion or embryo grafts was reported as far back as 1908 (Russell<sup>60h</sup> and confirmed subsequently.<sup>67</sup> Recent experiments on mice with substances isolated from the urine of a 4 year old girl seem to have yielded similar results.<sup>68</sup>

(c) Innervation of tissues. Another factor of great importance in determining organizer influence within tissues is the presence of nerve supply. The evidence for the close relation between the nervous system and local organizer function in the tissues lies in the sphere of growth and development, as well as in that of tumor formation.

A close relation is known to exist between the nervous system and organizer activity in the embryo, and it is difficult to imagine that this relation does not persevere in some form throughout the life of the individual. Its importance in lower forms has been clearly proved in the matter of regeneration. In earthworms and other annelids regeneration of highly individualized segments, such as the head, generally requires the presence of the main nerve cord.<sup>69</sup> Regeneration of a claw or leg in crabs and other crustaceans has recently been shown also to depend on a similar type of nervous integration. Since a mammal cannot reproduce a limb or similar unit of structure, the importance of the nervous system in regeneration is much less apparent. As far as I have found in the available literature, the factor of innervation has not yet been studied in regenerating tissues of mammals. It is theoretically conceivable that denervated tissues would show a tendency to over-

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65. As a rule in families affected by adenomatosis of the colon the tumors begin to develop at about the age of 20 years, and malignant changes may be expected about fifteen years later (Lockhart-Mummery, J. P., and Dukes, C. E.: *Familial Adenomatosis of Colon and Rectum: Its Relationship to Cancer*, *Lancet* **2**:586 [Sept. 9] 1939).

66. Sharpe, J. C., and Young, R. H.: *Recklinghausen's Neurofibromatosis: Clinical Manifestations in Thirty-One Cases*, *Arch. Int. Med.* **59**:299 (Feb.) 1937.

67. Murphy, J. B., and Sturm, E.: *A Factor from Normal Tissues Inhibiting Tumor Growth*, *J. Exper. Med.* **60**:293 (Sept.) 1934; *The Effect of a Growth-Retarding Factor from Normal Tissues on Spontaneous Cancer of Mice*, *ibid.* **60**:305 (Sept.) 1934.

68. Dobrovolskaïa-Zavadskaïa, N., and Zephiroff, P.: *Eket des produits d'origine épiphysaire et d'origine hépatique sur la croissance des tumeurs chez la souris*, *Compt. rend. Soc. de biol.* **134**:60, 1940.

69. Hyman, L. H.: *Aspects of Regeneration in Annelids*, in *Biological Symposia*, Lancaster, Pa., Jaques Cattell Press, 1941, vol. 2, p. 241.

regeneration, with production of hypertrophies. This should be tested experimentally. Schwannomas ("amputation neuromas"), which form in nerve stumps shortly after nerve section, can be induced to undergo prolonged growth if their normal reinnervation is prevented by avulsion of the nerve root (Masson <sup>70</sup>). Repeated section of the distal nerve stump is followed by growth of these experimental schwannomas to enormous size, with invasion of the surrounding muscles.

Masson has stressed the close interrelation between carcinoid tumors of the intestinal tract and neuromatous changes in the periglandular nerve plexus of the intestinal mucosa.<sup>71</sup> The frequent occurrence of carcinoid tumors in obliterated appendixes has drawn attention to their association with strangulation of nerve filaments and the consequent development of amputation neuromas. The carcinoid cells appear to arise from argentaffin cells of the intestinal epithelium <sup>71b</sup> and to gain a certain measure of autonomy of growth, possibly as a consequence of the perversion of nerve function. With rare exceptions these carcinoids are benign stationary growths; in the rare cases in which they exhibit invasive tendencies, the metastases are, with few exceptions, slow growing or stationary and show few of the features of aggressive malignancy.<sup>72</sup>

Congenital malignant neoplasms constitute a separate category from other tumors, according to Wells,<sup>64</sup> possibly by virtue of the peculiar metabolic properties of the tissues of their origin. Nearly all such tumors are sarcomas, and of these a large proportion are of neurogenic origin. Evidence is found that congenital maldevelopments of nerve tissues occur frequently, and these apparently may disappear, develop into malignant tumors, develop into benign tumors or even become malignant and then change in whole or in part into nonmalignant tissue. A large proportion of all neurogenic malignant tumors derived from the sympathetic nervous system and from the retina are present at birth, while congenital neoplasms of the brain and of the peripheral nerves are extremely rare (Wells <sup>64</sup>).

Recklinghausen's neurofibromatosis is marked by multiple benign tumors of the skin and internal organs in the course of peripheral nerves.

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70. Masson, P.: Experimental and Spontaneous Schwannomas (Peripheral Gliomas), *Am. J. Path.* **8**:367 and 389 (July) 1932.

71. Masson, P.: (a) Neural Proliferations in the Vermiform Appendix, in Penfield, W.: *Cytology and Cellular Pathology of the Nervous System*, New York, Paul B. Hoeber, Inc., 1932, vol. 3, sect. 25, p. 1095; (b) Carcinoids (Argentaffin-Cell Tumors) and Nerve Hyperplasia of the Appendicular Mucosa, *Am. J. Path.* **4**:181 (May) 1928.

72. Terplan, K.; Weintraub, D., and Wolf, N. J.: Stationary Metastasizing Carcinoid of the Ileocecal Valve, *Arch. Path.* **30**:1155 (Nov.) 1940. Ariel, I. M.: Argentaffin (Carcinoid) Tumors of the Small Intestine: Report of Eleven Cases and Review of the Literature, *ibid.* **27**:25 (Jan.) 1939. Bailey, O. T.: Argentaffinomas of the Gastro-Intestinal Tract, Benign and Malignant, *ibid.* **18**:843 (Dec.) 1934.

In addition, the disease exhibits peculiarities of development of isolated regions of the body, skeletal and visceral, which take the form of localized overgrowth or gigantism. It is probable that these are etiologically related to disturbances in innervation.

Timme (1913)<sup>73</sup> succeeded in producing marked hypertrophy of the stomach and colon experimentally in cats by partial interruption of both vagus nerves through constricting ligatures. Secretory, as well as motor, elements were increased in size and number; function, however, was greatly depressed. These experiments were cited by Scherer<sup>74</sup> in a discussion of the marked hypertrophy of the esophagus and stomach and of the giant appendix in the case of neurofibromatosis which he reported in which the vagus nerves were affected.

The latter disease presents a number of general parallels to the tuberous sclerosis complex as well, and these will be discussed later. One element in the disease which is of particular pertinence at this point of discussion is the frequent association of abnormalities of peripheral nerves with the development of sarcomas which may be highly malignant. The incidence of neurogenic sarcoma is said to range between 8 and 13 per cent of all cases.<sup>75</sup>

Ewing<sup>76</sup> cited Rindfleisch's opinion and the experiments of Remond and of Pearce and van Allen as evidence for the fact that defective nervous control is one of the factors predisposing to exaggerated growth of tissues and tumor formation.

There is much room for thought in regard to a possible mechanism by which nervous influences achieve an organizer effect on tissues. One may predicate, perhaps, a secretagogue-like nervous stimulation of specialized stromal cells subserving organizer function within organs. The effect, however, may be a direct one on all cells. The old concept of "trophic" nervous influence has an insecure factual basis but may possibly support analysis through this newer approach.

(d) Maldevelopment and the predisposition to tumor. One further factor involving organizer action in relation to neoplasia is the presence of developmental anomaly. The predisposition to malignancy of persistent embryonal remnants and malformations is an established principle.<sup>14</sup> Malignant tumors have been found in experimentally produced embryonic monsters as well; these tumors continue to grow and invade after transplantation into a normal animal.<sup>54a</sup> In the light of the researches already mentioned, it is possible now to trace a common background

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73. Timme, W.: Experimental Studies on the Nervous Mechanism in the Production of Hyperplasia, *J. Nerv. & Ment. Dis.* **40**:311, 1913.

74. Scherer, H. J.: Zur Frage des Zusammenhanges zwischen Neurofibromatose (Recklinghausen) und umschriebenem Riesenwuchs, *Virchows Arch. f. path. Anat.* **289**:127, 1933.

75. (a) Kaufmann,<sup>4</sup> vol. 2, p. 1568. (b) Sharpe and Young.<sup>66</sup>

76. Ewing,<sup>14</sup> p. 107.

for both developmental anomalies and tumors related to them in a perversion of organizers. The primary effect is a frustration of normal cell integration in certain areas, resulting in teratoid formations and embryonal rests; thereafter the local deficiency in organizers persists, and newly proliferated cells in later life are deprived of the normal impetus to maturation in these areas. Such cell districts may be said therefore to possess an increased susceptibility (or diminished "refractoriness") to the development of tumors. Thus the origin of certain malignant tumors in embryonal rests, as postulated by the Cohnheim-Ribbert theory,<sup>14</sup> is made consistent with the principle of defective induction of differentiation through faulty organizer mechanisms.

The "transition" of benign into malignant neoplasm is probably identical in principle with the theory of origin of cancer in embryonal rests. There is a growing tendency to separate benign tumors from the general category of neoplasms and to group them with growth anomalies. As Reimann<sup>77</sup> stated: "Benign growths have an organization, while malignant ones do not, and cellular differentiation in benign growths is quite different anatomically (and physiologically by presumption, for many reasons) from that in malignant growths." This is essentially the characterization of hamartoma,<sup>12</sup> which is a designation applied to many so-called benign tumors of organoid structure and, as already implied in this paper, is the underlying basis for the pathogenesis of the tuberous sclerosis complex. In a broad sense, therefore, predisposition to cancer may be regarded fundamentally as a fault in organizer action which permits cancer cells to spring into being, either directly from "irritated" reserve cells of mature tissues or in the course of a stepwise degradation of organizer potency, the first manifestation of which is an embryonal tissue defect (hamartia), succeeded in turn by a benign tumor (hamartoma) and eventually by a malignant tumor of slow or rapid evolution (hamartoblastoma).

The sequence of change from hamartia to hamartoma or to hamartoblastoma is probably not restricted to embryonic cells but may arise equally well in reserve cells of normal tissues at any period of mature life in the event of a defective process of regeneration. It is possible in this manner to explain the development of the hamartomas of adults, especially of old persons (fibromas, nevi, angiomas, etc.), as well as malignant mixed tumors of the testicle (hamarblastomas).

*The Organizer Principle in Relation to the Pathogenesis of the Tuberous Sclerosis Syndrome and Its Neoplastic Complications.*—With the foregoing generalizations in mind, one can quickly recognize in the tuberous sclerosis complex a particularly fortunate natural experiment

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77. Reimann, S. P., and Toennies, G.: Reaction of Mouse Skin to Various Reduced and Partially Oxidized Sulfur Compounds, *Arch. Path.* **29**:175 (Feb.) 1940.

for the testing of several implications of the organizer principle in human biology. As analyzed at present, the disease has its basis in a disseminated tissue malformation complicated by neoplastic overgrowths, chiefly in the brain. The basis for the ontogenetic fault may now be laid to a faulty sequence of interaction of organizers and cells rather than to cell defects alone, inasmuch as one of the truly important characteristics of the disease is its apparent inception in numerous widely scattered areas in a single interval of embryonal time. This fact reminds one of the manifold malformations ensuing in the frog embryo as a result of delayed fertilization<sup>54</sup> or in the chick embryo as a result of subnormal incubation temperature in the early hours after development has begun.<sup>53</sup> Furthermore, all gradations between normal and markedly abnormal cells have been shown to exist in affected areas, and the cytologic line of demarcation is often difficult to determine.

The organizer principle was utilized by Worster-Drought (1937)<sup>78</sup> in an analysis of the possible pathogenetic mechanism of several related syndromes of multiple tumor formation (Lindau's disease, tuberous sclerosis, neurofibromatosis, etc.) and, in particular, of 2 cases of multiple meningeal and perineural tumors (Wishart type of central neurofibromatosis). The implication of his analysis was that the mechanism of these disturbances was to be found in an excessive or unregulated organizer activity leading to multiple tumor or tumor-like formations. The importance of this generalization in aiding the interpretation of these syndromes cannot be overestimated.

Nevertheless, it is my belief that the primary emphasis should be placed not on excessive and indiscriminate organizer activity but on its frustration, either through intervening factors or through intrinsic defects in the cells themselves. Since, as already mentioned, the separate lesions of the disease exhibit throughout the body an unmistakable parallelism in their general features and in their chronology, a single biologic "incident" affecting many areas simultaneously is suggested. It is much more likely, for this reason, that the basic element in pathogenesis involves a disturbance in timing whereby the interaction of organizers and cells is disturbed at a certain crucial moment. Once that moment has passed, the organizers for specific inductions are superseded by new organizers and the cells of the affected regions are stranded, so to speak, in a condition of permanent embryonicity. In the hamartial foci which constitute the disease, the cells retain throughout life many of their original embryonal characters, exhibiting a singular inertia in the presence of later maturational influences. The appearance

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78. Worster-Drought, C.; Dickson, W. E. C., and McMenemey, W. H.: Multiple Meningeal and Perineural Tumours with Analogous Changes in the Glia and Ependyma (Neurofibroblastomatosis), with Report of Two Cases, *Brain* 60:85 (March) 1937.



of these lesions suggests, therefore, inhibition (minus formation) rather than stimulation (plus formation). The lesions, it is true, possess an imperfect architecture and in that respect simulate neoplasms. Nevertheless an organoid constitution is usually evident. The refractoriness to normal host influences is more marked in cells destined primarily for function rather than in those destined for support. The former elements may be scanty and poorly formed, as the abortive ganglion cells of the cerebral foci or the abortive tubules of the renal foci. The latter elements (mesenchyme, vasculature, glia) accordingly dominate the picture and produce the tumor-like bulkiness and nodularity of the lesions.

The question of malignancy in this disease is properly joined with that of its hamartial nature. In both respects, the heart of the problem is the defective activity of local organizers. From this standpoint, the factor of dysontogenesis, instead of predisposing to malignancy, as in cancer in general, seems to result in a relative antagonism to malignancy. It is difficult to resolve this apparent inconsistency on theoretic grounds, unless by the supposition that the abnormal cells, despite their embryonal structure, have nevertheless undergone as complete a differentiation as their limited competence permits and are thus incapable of proliferation endlessly in the manner of tumor cells. By the same token it is implied that these cells continue to respond to organizers within the master tissues after allowance is made for the gap in the organizer series to which they owe their malformation. The disorganizing factor of disturbed innervation, while much less important for the body as a whole than in multiple neurofibromatosis, is nevertheless prominent in the tuberous foci in the brain. As previously stated, there is a high incidence of malignant mixed tumors of the brain under such circumstances, and these are often multiple. In the other foci of the disease, malignancy is rare and is apparently restricted to the renal nodules. In their slow growth and restricted metastases their behavior is much more like that of carcinoids of the appendix than of malignant mixed tumors of the Wilms type.

#### TERMINOLOGY AND CLASSIFICATION OF THE TUBEROUS SCLEROSIS COMPLEX

These several considerations offer new possibilities in terminology and classification of the tuberous sclerosis complex. The disease may now be accepted, according to most studies, as a widespread developmental anomaly, often hereditary, in which the primary abnormality lies in the faulty differentiation of tissues rather than of body units (although the latter may be included). The individual lesions present the characters of hamartia or of hamartomas, regardless of their situation.

Because other organs are involved simultaneously with the brain, the term tuberous sclerosis, which refers only to the cerebral lesions, should be reserved for these and should not be employed to designate the syndrome as a whole. For the latter the term disseminated hamartiosis (Bourneville type) may be more suitable.

#### OTHER TYPES OF DISSEMINATED HAMARTIOSIS

*Multiple Neurofibromatosis.*—Reference should be made again to the numerous points of resemblance between the tuberous sclerosis complex and Recklinghausen's multiple neurofibromatosis. There is much discussion on this point,<sup>45</sup> and not a few writers regard the two diseases as related,<sup>79</sup> if not identical, in principle.<sup>80</sup>

This viewpoint is not shared by all, however. The common impression of the pathogenesis of the cutaneous and visceral nodules of neurofibromatosis is based on the studies of Verocay, who considered them benign neoplasms of the nerve sheaths. According to a later view, they are basically of more primitive origin (undifferentiated neuroepithelium<sup>75a</sup>) and originally contain both nerve cell and supporting cell elements, with the latter predominating and crowding out the former.

The point has also been raised that these nodules are hamartomas, i. e. malformations, which arise out of these primordial nerve elements,<sup>81</sup> and are therefore not true neoplasms. A number of gross malformations of more obvious character have also been described in this disease (epispadias, cryptorchidism, macroglossia, polythelia, bony and skeletal defects, infantilism),<sup>45</sup> adding much weight to the dysontogenetic interpretation. The high incidence of neurogenic sarcoma in this disease bears out notably the importance of two of the factors previously stated to interfere with organizer function—abnormal innervation and maldevelopment. The superimposition of both factors must a priori be expected to conduce to overgrowth and to neoplasia.

The palisaded nodules of the skin are classifiable as hamartomas of the Wagner-Meissner tactile corpuscles (Masson<sup>70</sup>) and the sarcomas of the soft parts as hamartoblastomas (fibrosarcoma, neurosarcoma) of the nerve sheaths. The regional hypertrophies associated with this disease

79. Globus, J. H.: Malformations in the Central Nervous System, in Penfield, W.: Cytology and Cellular Pathology of the Nervous System, New York, Paul B. Hoeber, Inc., 1932, vol. 3, p. 1150.

80. (a) Bielschowsky, M., and Gallus: Ueber tuberöse Sklerose, J. f. Psychol. u. Neurol. (Ergznzngshft.) 20:1, 1913. (b) Orzechowski, K., and Nowicki, W.: Zur Pathogenese und pathologischen Anatomie der multiplen Neurofibromatose und der Sklerosis tuberosa (Neurofibromatosis universalis), Ztschr. f. d. ges. Neurol. u. Psychiat. 11:237, 1912. (c) Yakovlev and Guthrie.<sup>28a</sup>

81. Sharpe and Young.<sup>65</sup> Masson.<sup>70</sup>

may be primary malformations (Pick<sup>82</sup>) or may be manifestations of the neurodystrophic deviation of organizer function. Such hypertrophies prove horribly disfiguring when they occur as localized elephantiasis of the face or of a limb.<sup>83</sup> Gigantism of the esophagus and stomach and segmental hypertrophy of the intestine<sup>84</sup> or appendix<sup>74</sup> have been recorded in association with changes in the vagus nerves and submucosal nerve plexuses.<sup>85</sup> Chromaffinoma of the adrenal glands<sup>86</sup> may even represent the effect of homologous changes in the sympathetic nerves and thereby furnish a close counterpart of the carcinoids of the appendix. Meningeal tumors, small foci of cortical gliosis and glioma-like tumors of the brain have been recorded in cases of neurofibromatosis and have given rise to the concept of central forms of the disease.<sup>87</sup> Defects in intelligence and infantilism have also been observed clinically.<sup>86</sup> In a few instances of multiple neurofibromatosis fragments of the tuberous sclerosis complex have also been noted, e. g., adenoma sebaceum<sup>80a</sup> and phacoma of the retina,<sup>85</sup> but otherwise the hamartial tendency is confined to the structures already described.

*Lindau's Disease and Related Syndromes.*—In an adjacent category may be placed the complex known as Lindau's disease.<sup>88</sup> This syndrome presents a distinctive type of retinal angiomas (von Hippel's disease) with associated angiomas of the cerebellum, brain stem and spinal cord. The cerebellar angiomas may become cystic and are prone to recurrent hemorrhage, which may cause sudden death. Cysts of the kidney and pancreas are frequent, as are also adenomas or "hypernephromas" of the kidney. Like tuberous sclerosis and neurofibromatosis, Lindau's disease occurs as a mendelian dominant and is thus both hereditary and familial. The angiomas of this disease may be regarded as hamartomas of vascular type occurring within a restricted organ distribution.

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82. Pick, L.: Ueber Neurofibromatose und partiellen Riesenwuchs, mit mesenterialer Neurofibromatose, insbesondere über die sektorenförmige Kombination von wahren partiellen Riesenwuchs des Darmes, Beitr. z. path. Anat. u. z. allg. Path. **71**:560, 1923.

83. Ewing,<sup>14</sup> p. 164. Sharpe and Young.<sup>65</sup>

84. Lotz, A.: Der partielle Riesenwuchs mit besonderer Berücksichtigung des sogenannten sekundären, eine pathologisch-anatomische Untersuchung, Inaug. Dissert., Berlin, G. Schade, 1914.

85. Scherer.<sup>74</sup> Pick.<sup>82</sup> Lotz.<sup>84</sup>

86. Rosenthal, D. B., and Willis, R. A.: The Association of Chromaffin Tumours with Neurofibromatosis, J. Path. & Bact. **42**:599 (May) 1936.

87. Worster-Drought, Dickson and McMenemy.<sup>78</sup> Footnote 80a and b.

88. Lindau, A.: Studien über Kleinhirncysten: Bau, Pathogenese, und Beziehungen zur Angiomatosis retinae, Acta path. et microbiol. Scandinav., 1926, supp. 1, p. 1. Cushing and Bailey.<sup>7a</sup>

It is not unlikely that heredofamilial angiomas of the skin and mucosa (Osler's disease<sup>89</sup>) is based on the same dysontogenetic principles. Another complex has been described, encephalotrigeminal angiomas, which suggests some of the general features of tuberous sclerosis.<sup>90</sup> Its outstanding features are naevus vasculosus of the face in the distribution of the fifth cranial nerve, slight angiomas of the pia mater and aplasia, sclerosis and calcification of parts of the cerebral cortex. Clinically one notes epilepsy, mental retardation and slight spastic hemiplegia contralateral to the facial nevus.

Congenital polycystic disease should also be grouped among the disseminated hamartioses. In its histopathologic features can be clearly recognized a diffuse hamartial disturbance affecting the duct pattern of one or more organs, leading to the formation of cysts. Although its most frequent manifestation is in the kidneys, it involves the liver frequently<sup>90a</sup> and less often the pancreas and other organs. It is a heredo-familial disorder and is frequently associated with other developmental anomalies (harelip, meningocele, polydactyly, spina bifida).

*Irregular Types of Hamartiosis.*—A number of individual cases are on record of a disseminated hamartial type of maldevelopment in which classification among well defined syndromes cannot be made. Three cases of congenital muscular hypertrophy, extrapyramidal motor disturbances and mental deficiency were reported by de Lange.<sup>91</sup> Peculiar changes in the convolutions (polygyria, microgyria), partial underdevelopment of certain parts of the brain and overdevelopment of others and widespread microscopic porencephaly were among the features found at autopsy in 1 case. Weil<sup>92</sup> reported a case of familial megalencephaly in a boy aged 7 whose brain weighed 1,856 Gm. In addition to the interstitial hypertrophy of the cerebrum (glial hypertrophy) the brain stem and cerebellum presented diffuse "glioblastomatosis." The precentral area was poorly developed. The skeletal muscles were also underdeveloped. The medulla of the adrenal glands was practically devoid of chromaffin tissue. Stewart reported a case of muscular dystrophy with feeble-mindedness, pronounced vagotonia, hypertrophy of

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89. Madden, J. F.: Generalized Angiomas (Telangiectasia), J. A. M. A. **102**: 442 (Feb. 10) 1934.

90. Krabbe, K. H.: Facial and Meningeal Angiomas Associated with Calcifications of the Brain Cortex, Arch. Neurol. & Psychiat. **32**:737 (Oct.) 1934. Yakovlev and Guthrie.<sup>28a</sup>

90a. Moolten, S. E.: Congenital Anomalies of the Smallest Bile Ducts, to be published.

91. de Lange, C.: Congenital Hypertrophy of the Muscles, Extrapyramidal Motor Disturbances and Mental Deficiency, Am. J. Dis. Child. **48**:243 (Aug.) 1934.

92. Weil, A.: Megalencephaly with Diffuse Glioblastomatosis of the Brain Stem and the Cerebellum, Arch. Neurol. & Psychiat. **30**:795 (Oct.) 1933.

the salivary glands and peculiar warty nodules of glial hyperplasia in the cerebral cortex which suggested an unusual type of "primary gliosis" rather than an abortive form of tuberous sclerosis.<sup>93</sup> These and similar conditions are perhaps conveniently grouped as disseminated hamartioses of irregular type. Again, as in the tuberous sclerosis complex, the most noteworthy error of development is found in the nervous system.

#### SUMMARY

A case of the tuberous sclerosis complex in a girl aged 20 is described. The disease was first brought to light clinically by hemorrhage from a renal hamartoma. The latter was of striking appearance but typical histologic structure and contained a large angiomatic component and a caliceal anomaly. The patient also presented adenoma sebaceum, phacoma of the retina and clinical evidences of typical cerebral involvement. The course of her later illness resembled that of a tumor involving the brain stem in the region of the left corpus quadrigeminum and aqueduct of Sylvius. Left ophthalmoplegia with Argyll Robertson pupil were present, also papilledema and other evidences of internal hydrocephalus.

The tuberous sclerosis complex may be epitomized as a disseminated disease, often heredofamilial in type, characterized by numerous defects in tissue combination (hamartia). The brain, heart, retina, kidneys and skin are conspicuously affected. The individual lesions range in size from microscopic foci (hamartial "germs") to visible nodules (hamartomas) having a superficial resemblance to neoplasms. Developmental defects of a more serious type, such as cardiac or renal anomaly and so-called stigmas of degeneracy, often coexist and corroborate the view that the disease has its inception in the earliest stages of embryonal development.

Malignant neoplasms supervene with extreme rarity in the somatic foci of the disease and are slow growing and produce few metastases. In the cerebral foci, however, such tumors appear to occur much more frequently, taking the form of a malignant mixed tumor (neurospongioblastoma), which is often multiple.

The concept of a defective mechanism of induction by embryonic organizers (Spemann) offers a logical explanation of the pathogenesis of this disease and of the accompanying developmental defects. There is much reason to believe that the same principle underlies the later complication of malignancy, especially in the brain. In a study of this disease as a type it is possible to derive certain generalizations which have application to problems of more general importance, chiefly the genesis of congenital dysplasia and the predisposition to tumor. The

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93. Stewart, R. M.: An Unusual Type of Cortical Gliosis, *J. Neurol. & Psychopath.* **15**:160 (Oct.) 1934.

embryonic systems of organizer action are probably the initial phase of certain basic mechanisms of cellular integration which normally govern differentiation and maturation of proliferating cells throughout life. Excessive fibrosis, aging and preexisting malformation are factors which evidently impair such control and thereby predispose to malignancy. Neurotrophic influences are apparently also important in the maintenance of the organizer field, and the predisposition to brain tumor in tuberous sclerosis is probably only one of many instances in which defects in neural integration underlie the predisposition both to anomalous overgrowth and to neoplasia.

The similarities between the tuberous sclerosis complex, multiple neurofibromatosis, encephalotrigeminal angiomas, Lindau's disease and related syndromes are sufficient to establish them all as forms of disseminated hamartiosis. The latter term may be employed as a general category of classification for syndromes such as these in order to emphasize their non-neurologic features.

# ACUTE BACILLARY DYSENTERY

## A CLINICOPATHOLOGIC STUDY OF TWO HUNDRED AND SIXTY-THREE CONSECUTIVE CASES

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CRISTOBAL, CANAL ZONE

During the past eleven years, from Jan. 1, 1930, to Jan. 1, 1941, 263 cases of acute bacillary dysentery have been recorded at the Gorgas Hospital. In all cases this diagnosis was confirmed by stool cultures positive for the causative organism. It was felt that a careful study of this group of cases might be of some value in a better understanding of the disease. No attempt at an exhaustive review of the literature has been made.

Felsen<sup>1</sup> stated in 1939 that there was a rising incidence of bacillary dysentery in the United States, the reported figures for 1937 being approximately sixteen times those for 1933. He also pointed out that as the reported cases of bacillary dysentery increase there is a corresponding decline in the number of cases of unclassified "diarrhea and enteritis." During the period covered by this survey 3,556 cases of unclassified "diarrhea and enteritis" have been recorded at the Gorgas Hospital, while only 263 cases of bacillary dysentery and 240 cases of amebic dysentery have been reported.

### INCIDENCE

The cases were distributed throughout the period as shown in table 1. There was a rather marked rise in the number of reported cases beginning in 1935. The incidence for 1930 is possibly somewhat misleading because of the occurrence of an epidemic during that year, which will be referred to later. There was no significant seasonal variation. The age distribution is shown in chart 1. The number of patients less than 1 year old was small and peaks were reached between the ages of 1 and 5, and 21 and 25. There was a significant difference in sex

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Read at the January 1941 meeting of the Isthmian Medical Society, Panama, Republic of Panama.

1. Felsen, J.: Newer Concepts of Intestinal Infection, J. A. M. A. **112**:46-49 (Jan. 7) 1939.

incidence, with males outnumbering females almost 2:1 (table 2). The relation of color and nationality to the disease was of less importance.

In 26 of these 263 cases, such obvious complicating and wholly distinct disease processes were apparent at the time of admission to the hospital that those cases were not included in the clinical study. This leaves 237 cases which were so studied.

TABLE 1.—*Date of Onset*

Year	No. of Cases	Month	No. of Cases
1930.....	33	January.....	26
1931.....	3	February.....	53
1932.....	8	March.....	29
1933.....	3	April.....	12
1934.....	3	May.....	13
1935.....	16	June.....	22
1936.....	45	July.....	17
1937.....	28	August.....	10
1938.....	52	September.....	19
1939.....	44	October.....	18
1940.....	28	November.....	22
		December.....	22

TABLE 2.—*Relation of Sex, Color and Nationality to Incidence of Acute Bacillary Dysentery*

	No. of Cases	Percentage
<b>Sex</b>		
Male.....	170	64.7
Female.....	93	35.3
<b>Color</b>		
Negro.....	149	50.6
Native white.....	110	41.8
Foreign white.....	4	1.5
<b>Nationality</b>		
Panamanian.....	100	38.0
American.....	93	35.3
West Indian.....	55	20.9
Others.....	15	5.7

#### NUMBER OF DAYS BETWEEN ONSET OF SYMPTOMS AND ADMISSION TO HOSPITAL

The period of incubation could not be determined, as in no case was the exact time of exposure known. Woolpert and associates<sup>2</sup> reported a case in which the disease occurred in a laboratory worker as a result of accidental inoculation and in which the incubation period

2. Woolpert, O. C.; Marsh, H. F., and Yaw, O. F.: Bacillary Dysentery Accidentally Incurred in the Laboratory, J. A. M. A. **113**:753-754 (Aug. 26) 1939.



could be accurately determined as forty-eight hours. Table 3 shows the number of days during which symptoms had been present before the patient entered the hospital; 33 per cent entered during the first twenty-four hours of disease, while 94 per cent entered during the first seven days.

#### SYMPTOMS AND PHYSICAL FINDINGS

The symptoms complained of are recorded in chart 2. The word dysentery carries with it an implication of diarrhea. Actually this complaint was elicited in only 80 per cent of all cases, and in 4 per cent such a manifestation was specifically denied. Smith<sup>3</sup> studied an epidemic of Sonne dysentery, occurring in England in 1931, in which diarrhea was present in only 57 per cent of the cases. The number of stools varied from one to sixty per day. The presence of gross blood in the stool was observed and reported by the patient in 48 per cent of

	0	5	10	15	20	25	30	35	40	45	50	total	percentage
under 1												5	1.9
1-5												45	17.2
6-10												9	3.4
11-15												10	3.8
16-20												18	6.8
21-25												39	14.8
26-30												29	11.0
31-35												22	8.4
36-40												24	9.2
41-45												16	6.0
46-50												14	5.4
51-55												14	5.4
56-60												8	3.0
61-65												7	2.7
66-70												1	0.4
71-75												2	0.8

Chart 1.—Age incidence of 263 cases of acute bacillary dysentery.

TABLE 3.—Interval Between Onset of Symptoms and Admission to Hospital

No. of Days	No. of Cases
1.....	74
2.....	26
3.....	38
4.....	27
5.....	22
6.....	10
7.....	11
8.....	4
9.....	1
10.....	3
14.....	3
Over 14.....	4

the cases. Abdominal pain, which was commonly present, manifested itself as a crampy pain occurring anywhere along the course of the

3. Smith, R. E.: A Clinical Description of Epidemic Sonne Dysentery, *Lancet* 2:925-927 (Oct. 24) 1931.

colon and was poorly localized. Convulsions were reported by 8 patients, all of whom were children with high fever.

The only physical finding of importance was abdominal tenderness, which varied from slight to rather marked. This was present in 52 per cent of all cases. In some it was accompanied by voluntary spasm of the abdominal wall, but in no case was true rigidity noted. There was some tendency to localization in the lower quadrants, but in most cases it was present diffusely, and there was no significant difference between the two sides of the abdomen. Abdominal distention was encountered only rarely and was always mild.

No attempt was made to classify these cases according to such arbitrarily designated types of disease as "meningitic," "pneumonic" or "appendicular," as it was felt that such terms do not signify sharply defined clinical entities. It will be understood that the clinical picture does vary somewhat from case to case, as is true in all diseases, depending on the predominance of one or more of the various symptoms and signs.

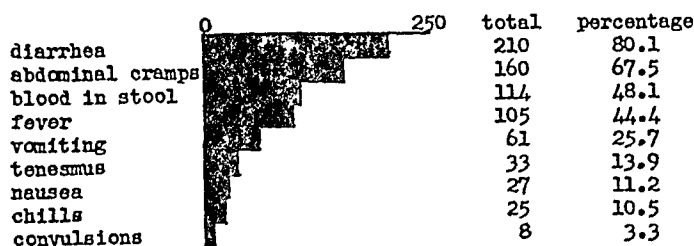


Chart 2.—Incidence of diarrhea in 263 cases of acute bacillary dysentery and incidence of other symptoms in 237 cases of the disease.

#### LABORATORY FINDINGS

The total white blood cell count was recorded in 224 cases (chart 3). It varied rather widely, with extremes of 2,000 and 58,000, but in 90 per cent of cases it was between 4,000 and 13,000. The average figure was 8,760. The differential count was recorded in 217 cases (chart 4). It also varied widely. The number of neutrophilic granulocytes varied from 10 to 95 per cent of the total, but in 72 per cent of all cases it was between 60 and 85 per cent. The average was 67 per cent. The number of lymphocytes varied correspondingly, with an average of 33 per cent. Eosinophils were present in normal number, with an average of 0.9 per cent. The erythrocyte counts and hemoglobin determinations were not remarkable in any way and did not indicate the presence of significant dehydration. From these figures it can be seen that the blood count is not of much value in making a diagnosis of acute bacillary dysentery, as high, low or normal values may be present.

In 11 cases blood cultures were made; all were negative for the dysentery bacillus. It is generally agreed that blood cultures are of no value in diagnosis and that bacteremia is present only rarely.

In only 5 cases were agglutination tests performed. This number was so small that further study was not made and no conclusions can be drawn. Such tests are not of much value in diagnosis of the acute

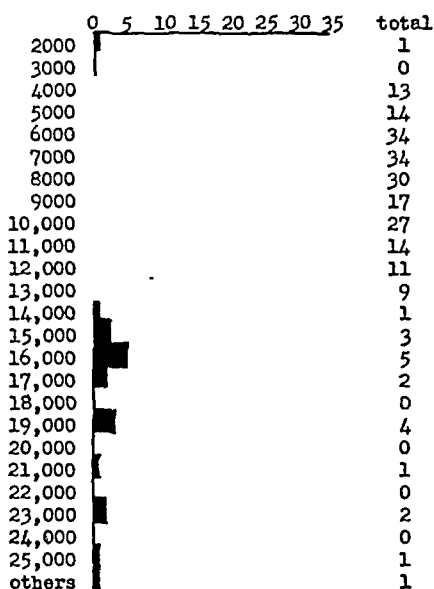


Chart 3.—White blood cell counts in 224 cases of acute bacillary dysentery.

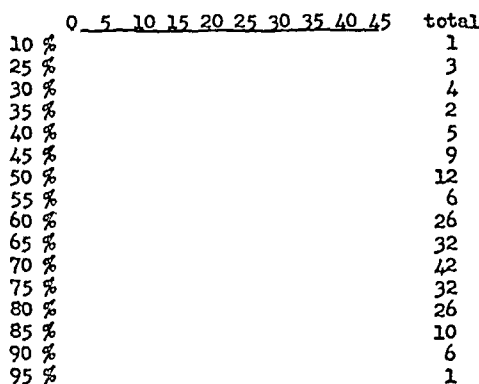


Chart 4.—Percentages of neutrophilic granulocytes in 217 cases of acute bacillary dysentery.

disease, since agglutinins do not appear in the blood stream until relatively late in the course of illness.

The results of gross and microscopic examination of the stools are given in table 4. The number of patients with blood, pus or mucus in the stools was not as high as might be expected. A possible explanation for this is the likelihood that many patients with a more benign form

of the disease may have entered the hospital too late in the course of illness for these substances to be found in a routine examination.

In 8 cases samples of urine were cultured; all were negative for the dysentery bacillus. In 3 cases, because of the presence of convulsions, spinal puncture was performed and the spinal fluid was cultured; all cultures were negative for the dysentery bacillus.

Wide differences of opinion exist regarding classification of the various dysentery bacilli, and there are several methods in use today. In this hospital the dysentery bacilli are classified as belonging to one of three groups, as follows:

*Group 1:* Non-mannitol-fermenting bacilli. *Bacillus dysenteriae* Shiga is the most important member of this group and is the only

TABLE 4.—Results of Examination of Stools \*

Substance	No. of Cases	Percentage
Pus.....	159	79.5
Blood.....	131	65.5
Mucus.....	107	53.5

\* One hundred and ninety-eight patients were examined.

TABLE 5.—Incidence of Strains of Dysentery Bacilli

Strain	No. of Cases	Percentage
Group 1.....	0	
Group 2.....	240	91.2
Group 3.....	17	6.5
Atypical.....	4	1.5
Mixed.....	2	0.8

dysentery bacillus known to produce an exotoxin. It possesses a distinctive type antigen.

*Group 2:* Mannitol-fermenting bacilli which do not ferment lactose and saccharose. *Bacillus dysenteriae* Flexner is the most generally known member of this group, but many other allied but slightly different strains have been described by Hiss, Russell, Strong, Musgrave and others.

*Group 3:* Mannitol-fermenting bacilli which are late fermenters of lactose and saccharose. The only known pathogenic member of this group is *Bacillus dysenteriae* Sonne.

Clinically bacillary dysentery may be divided into two types: (a) that due to infection with the Shiga bacillus, usually associated with a severe, toxic course and a high mortality, and (b) that due to any of the other strains, which characteristically induce a milder illness, with a much lower mortality.

The organisms recovered in the 263 cases are shown in table 5. It is of interest that no cases of infection with the Shiga bacillus were

encountered. Conner and Bates studied 66 cases of bacillary dysentery occurring in this hospital during the five year period from 1919 to 1923 and found that in 4 of the 66 infection was due to the Shiga bacillus.<sup>4</sup>

#### SIGMOIDOSCOPIC FINDINGS

One hundred and thirty-three, or 51 per cent, of all patients were examined by means of the sigmoidoscope on one or more occasions during their stay in the hospital. The reports submitted by the examiner are summarized in table 6. The percentage of positive findings was somewhat low. In many cases, however, the patient was examined only once, and in some cases this was done relatively late in the course of the disease. In a few instances the report simply read "characteristic of bacillary dysentery." Ulcers were observed in only 53 per cent of the patients examined.

TABLE 6.—*Results of Sigmoidoscopic Examination \**

Condition	No. of Cases	Percentage
Hyperemia.....	89	66.9
Ulcer.....	77	52.6
Edema.....	31	23.3

\* One hundred and thirty-three examinations were made.

#### TREATMENT

Symptomatic measures were employed in all cases. This usually consisted of rest in bed, the administration of fluids and a simple liquid or low residue diet. In most cases an initial saline purge was given. Bismuth salts and camphorated tincture of opium were given almost routinely. In many cases scraped apple or pectin was given in varying quantity. In those cases in which sigmoidoscopic examination revealed a badly ulcerated rectum or sigmoid, local irrigation with a solution of tannic acid, silver nitrate or potassium permanganate was employed. The clinical evaluation of these many therapeutic measures does not lend itself well to statistical study. This is due to the multiplicity of measures employed, the lack of detailed comment on the progress of the patient and the impossibility of selecting a controlled series for the study of any one measure. No conclusions can be drawn.

Beginning in 1935, serum in the form of a polyvalent antidysentery preparation was employed. After that year such treatment was given

4. Conner, R. C., and Bates, L. B.: A Clinical and Bacteriological Analysis of the Cases of Bacillary Dysentery in Ancon Hospital During 1919 to 1923, *Internat. Clin.* 4:34-47 (Dec.) 1924.

in 71.8 per cent of all cases, or 52 per cent of all cases in the series. It is unfortunate that the same serum preparation was not employed throughout this period. Instead, lots from several pharmaceutic houses were carried in stock at different times. In general it can be said that all consisted of immune serums obtained from horses which had been inoculated with several of the more common dysentery bacilli. The dose employed varied with several factors, depending on the age of the patient, the severity of the disease and the duration of the disease before treatment was instituted. In general, however, the amount varied from a total of 80 to 200 cc., given in several divided doses of 20 to 40 cc. by the intramuscular and/or the intravenous route. The dose for children was scaled accordingly.

It can be seen that as regards mortality, average number of days in the hospital and average number of febrile days, the serum-treated patients compare unfavorably with those who were not so treated (chart 5). The actual significance of these figures must be questioned,

Mortality		
A		6.5 %
B		7.5 %
C		5.5 %
Hospital Days		
A		13.4
B		14.5
C		12.3
Febrile Days		
A		5.3
B		6.6
C		4.0

Chart 5.—Mortality, duration of stay in the hospital and duration of fever in the entire series of 263 cases (A), in 133 cases in which serum therapy was employed (B) and in 130 cases in which such therapy was not employed (C).

in view of the fact that, in general, the more seriously ill patients were selected for serum treatment whereas the patients with more benign disease were not so treated. Nevertheless, from the data collected, it cannot be said that the use of serum materially benefited the group of patients which were so treated.

A study of the available literature readily reveals that a wide difference of opinion exists regarding the efficacy of serum treatment of bacillary dysentery. Results of controlled studies are not available. The evidence regarding its use in cases of infection produced by the Flexner and Sonne organisms is particularly scanty. Striking results, with a reduction of mortality by 50 per cent and more in a group of cases produced by all dysentery bacilli, have been reported by Willmore and Savage.<sup>5</sup> Graham<sup>6</sup> stated that the mortality was reduced

5. Willmore, J. G., and Savage, H.: The Diagnosis and Treatment of Epidemic Bacillary Dysentery, *Brit. M. J.* 2:1283-1286, 1913.

6. Graham, D.: The Diagnosis and Treatment of Bacillary Dysentery Occurring in the British Salonika Force, *Lancet* 1:51-55 (Jan. 12) 1918.

to 1 per cent in 200 cases in which treatment was with serum. Acton and Knowles,<sup>7</sup> however, stated that the use of serum is of value only in infections caused by the Shiga bacillus. The most striking effect of serum therapy is its antitoxic effect in highly toxic patients, the majority of whom are infected with the Shiga bacillus. Cases of infection by this bacillus are not included in this study (table 5). Patients whose disease was of average severity or mild frequently respond with definite improvement, but since they are likely to improve in any case, the possibility of serum sickness and the expense of the serum must be considered before such therapy is attempted for them.

### FEVER

In classifying these cases according to the height of fever, the predominant range of temperature was recorded, rather than the highest point reached. Eleven per cent of the patients were afebrile throughout their entire stay in the hospital. Conner and Bates<sup>4</sup> reported that

TABLE 7.—*Incidence of Fever*

Degree of Fever	Temperature, F.	No. of Cases	Percentage
None.....	.....	26	11.0
Low.....	98.6 to 100	51	21.7
Moderate.....	100 to 102	83	35.3
High.....	102 and over	75	31.9

nearly 10 per cent of their patients were afebrile. It can be seen that the patients with fever were distributed rather evenly through the low, moderate and high ranges (table 7).

### DURATION OF HOSPITALIZATION

The number of hospital days for the entire series varied from three to thirty-seven, averaging thirteen and four-tenths. The number of febrile days varied from none to thirty-four, averaging five and three-tenths. It is evident that the disease, as it occurs on the Isthmus of Panama, is not incapacitating as regards length of stay in the hospital.

### MORTALITY

Available statistics indicate that the mortality varies greatly in different localities and epidemics. The recorded figures run from 1 per cent to as high as 50 per cent. In the five year survey of cases occurring in this hospital during the years 1919 to 1923, previously referred to, the mortality rate was 28 per cent.<sup>4</sup> In the present series

7. Acton, H. W., and Knowles, R.: On the Dysenteries of India, Calcutta, Spink & Co., 1923.

of 263 cases there were 17 deaths, a mortality rate of 6.5 per cent. The mortality rate for the 237 cases in which there were no complications was 5.1 per cent (12 deaths). The number of days of hospitalization before death varied from one to nineteen and averaged six. In an attempt to evaluate the various factors concerned, the cases were grouped as shown in table 8. There was no variation between the sexes. The mortality among Negro patients was almost twice that among white patients. Age was of great importance. The greatest mortality was among the aged (40 per cent), with that among children occupying an intermediate position and with an exceedingly low death rate among all patients between the ages of 6 and 60 (2.4 per cent). The death rate among patients infected with the Sonne bacillus was

TABLE 8.—*Mortality*

	Percentage
Entire series.....	6.5
Sex	
Male.....	6.5
Female.....	6.5
Color	
Negro.....	8.1
White.....	4.5
Nationality	
British West Indian.....	10.9
Panamanian.....	8.0
American.....	2.2
Age, Years	
Under 1.....	20.0
1 to 5.....	15.5
6 to 60.....	2.4
Over 60.....	40.0
Dysentery bacilli	
Group two.....	6.3
Group three.....	11.8

almost twice that among patients infected with organisms belonging to the Flexner group.

#### EPIDEMIOLOGY

During the period studied there was only one true epidemic occurring in the Canal Zone. This was in February 1930, when over a period of thirteen days, 33 patients with acute bacillary dysentery were admitted to the hospital from the United States army posts of Corozal and Davis. In all cases infection was due to organisms belonging to the Flexner group and was relatively mild. There were no deaths. The cause of this epidemic was not determined.

It is likely, however, that infection in this epidemic, as well as in many isolated cases included in this study, was due to carriers. In a recent survey of all food handlers employed in the United States army posts of the Canal Zone, a total of 2,206 persons were subjected to



routine stool cultures. Of these, 5 were found to be carriers of dysentery bacilli. Two harbored bacilli of the Flexner type, while 3 carried bacilli of the Sonne type.

#### PATHOLOGY

Autopsy was performed in 13 (70 per cent) of the 17 fatal cases among the 263 cases in this series. One case was discarded because of the presence of pulmonary and intestinal tuberculosis. An additional 19 cases occurring before 1930 were added from the files. Thus a total of 31 autopsy protocols were studied.

Gross pathologic changes were recognized in 97 per cent of all cases, and the small intestine was involved almost as commonly as was the colon (table 9). The characteristic changes are confined to the colon and the lower portion of the ileum. The earliest change consists of enlarged lymph follicles standing out like grains of sand on a reddened

TABLE 9.—*Distribution of Gross Pathologic Lesions*

	No. of Cases	Percentage
Number of autopsies.....	31	
Gross changes recognized.....	30	97
Large intestine.....	29	93
Entire colon.....	24	
Cecum only.....	3	
Scattered.....	2	
Rectum only.....	1	
Small intestine.....	22	71
Distance from ileocecal valve.....	10 to 200 cm.	
Average.....		70 cm.

background of inflamed mucosa. Within a short time the centers of the follicles become necrotic, so that multiple miliary ulcers are produced. This necrosis is progressive, so that widespread, discrete and confluent ulceration is seen. The ulceration is not deep as a rule, and only rarely is the muscularis involved (4.5 per cent). The mucosa and submucosa, however, are necrotic over large areas, and in many cases (45 per cent) a well developed pseudodiphtheritic membrane is formed.

Microscopic sections of the intestine show a heavy infiltration with neutrophilic granulocytes, lymphocytes and macrophages. This commonly involves the submucosa and muscularis and may extend to the serosa (14 per cent). As the process continues the coagulation necrosis becomes less marked, and small round cell infiltration is more prominent. Still later, granulation tissue may be observed growing up from the base of the ulcerated areas. These heal by extension of neighboring epithelium.

## SUMMARY AND CONCLUSIONS

Data compiled from a study of 263 consecutive cases of acute bacillary dysentery have been presented.

The disease occurred among persons of each sex and of every age, color and nationality, but it predominated in Negroes (57 per cent), males (65 per cent) and patients aged 1 to 5 (17 per cent) and 21 to 25 (15 per cent).

Diarrhea, abdominal cramps, gross blood in the stool and fever were the most common symptoms, in the order given.

The total white blood cell and differential counts varied widely. The average for each was well within normal limits.

The organisms recovered from the stools consisted entirely of members of the Flexner (91 per cent) and the Sonne (6.5 per cent) group. No cases of infection with the Shiga bacillus were encountered.

Polyvalent serum therapy was employed in 52 per cent of all cases but was not adequately controlled in any sense. A study of the serum-treated, as compared with the non-serum-treated, patients failed to reveal evidence indicating that such therapy had been of value.

The mortality for the entire series was 6.5 per cent. It was greatest among the aged (40 per cent), with that among children occupying an intermediate position (15 to 20 per cent) and with an exceedingly low rate among all patients aged 6 to 60 (2.4 per cent). The mortality in cases of infection caused by the Sonne bacillus (11.8 per cent) was greater than in cases of infection caused by the Flexner bacillus (6.3 per cent).

The characteristic pathologic picture, as determined by a study of 31 autopsy protocols, has been described.

# CHEMOTHERAPY AND CHEMOSEROTHERAPY OF STAPHYLOCOCCIC INFECTIONS

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AND

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WITH THE TECHNICAL ASSISTANCE OF ANNA M. RULE  
PHILADELPHIA

Until the discovery of sulfanilamide and its derivatives chemotherapy had little of proved value to offer in the treatment of staphylococcic infections. It is true that recoveries from staphylococcic septicemia in human beings have been ascribed to the intravenous administration of gentian violet, neutral acriflavine and various mercurial and other compounds, but none of these substances has materially reduced its high mortality and none has proved of value in the treatment of experimental infections of mice and rabbits under well controlled conditions.

Domagk<sup>1</sup> found the original prontosil (the hydrochloride of 4-sulfamido-2'-4'-diaminoazobenzene) somewhat effective in the treatment of experimental staphylococcic infections of mice and later reported<sup>2</sup> that better results were observed with uliron (a brand of dimethyldisulfanilamide; paraaminobenzenesulfonylparaaminobenzenedimethylsulfonamide). As shown in table 1, various investigators have found sulfanilamide, sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) and, more recently, thiazole derivatives of sulfanilamide effective in varying degrees in the treatment of these experimental infections. Sulfapyridine has been found somewhat more effective than sulfanilamide, while sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) has proved more effective than sulfapyridine. The first published report on the therapeutic use of the original prontosil was that of Foerster,<sup>3</sup> who treated a child with staphylococcic septicemia; the child recovered. Since

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From the Research Institute of Cutaneous Medicine.

1. Domagk, G.: Ein Beitrag zur Chemotherapie der bakteriellen Infektionen, *Deutsche med. Wchnschr.* **61**:250, 1935.

2. Domagk, G.: Weitere Untersuchungen über die chemotherapeutische Wirkung sulfonamidhaltiger Verbindungen bei bakteriellen Infektionen, *Klin. Wchnschr.* **16**:1412, 1937.

3. Foerster: Sepsis im Anschluss an ausgedehnte Periporitis: Heilung durch Streptozon, *Zentralbl. f. Haut- u. Geschlechtskr.* **45**:549, 1933.

then it is astonishing that so few clinical results have been published,<sup>4</sup> but we surmise that this is not because the prontosils, sulfanilamide and sulfapyridine have failed to be employed but because the results have been poor and failures are so seldom reported.

It is true that sulfathiazole has proved more effective in the treatment both of local infections and of septicemia caused by staphylococci, with a material reduction in the mortality of the latter, but the chemotherapy of severe staphylococcic infections is by no means a solved problem, and

TABLE 1.—*Previous Reports of Experimental Infections with Staph. Aureus Induced in Mice and Treated with Sulfanilamide or a Derivative*

Author	Compound	Animals Treated		Controls	
		No.	Survival, %	No.	Survival, %
Buttle, G. A. H.: Proc. Roy. Soc. Med. <b>31</b> : 154, 1937	Sulfanilamide	30	50	10	0
Mellon, R. R.; Shinn, L. E., and McBroom, J.: Proc. Soc. Exper. Biol. & Med. <b>37</b> : 563, 1937	Sulfanilamide	21	38	21	14
Feinstone, W. H., and others: Bull Johns Hopkins Hosp. <b>62</b> : 565, 1938	Sulfanilamide	50	34	50	10
Whitby, L.: Lancet <b>2</b> : 1095, 1938.....	Sulfapyridine	40	15	18	16
	Sulfapyridine	80	7.5	..	..
Bliss, E. A., and Long, P. H.: Proc. Soc. Exper. Biol. & Med. <b>40</b> : 32, 1939	Sulfanilamide	50	8	30	0
	Sulfapyridine	49	33	..	..
Barlow, O. W., and Homburger, E.: Proc. Soc. Exper. Biol. & Med. <b>42</b> : 792, 1939	Sulfathiazole	20	70	20	0
	Sulfamethylthiazole	20	90	..	..
	Sulfaphenylthiazole *	20	45	..	..
	Sulfapyridine	20	30	..	..
Rake and McKee <sup>5</sup> .....	Sulfapyridine	150	12	150	4.3
	Sulfathiazole	150	63.3	..	..
	Sulfamethylthiazole	150	52	..	..

\* 2-(paraaminobenzenesulfonamido)-4-phenylthiazole.

none of the drugs of the sulfanilamide group has proved as effective as some of them are known to be in the treatment of hemolytic streptococcic infections.

There is therefore an urgent need for further efforts in the chemotherapy of staphylococcic septicemia. And this is particularly true since both mice and human beings may recover from the septicemia only later to succumb to pyemic abscesses in the kidneys or other organs. In other

4. Kolmer, J. A.: Progress in Chemotherapy of Bacterial and Other Diseases with Special Reference to Prontosils, Sulfanilamide and Sulfapyridine, Arch. Int. Med. **65**:671 (April) 1940.

words, sulfanilamide or one of its derivatives may effectively remove staphylococci from the blood but fail to disinfect the fixed tissues. This has also been shown to occur in experimental infections of mice, so that survival of animals for two to four weeks may not really indicate cure or complete recovery. For example, Rake and McKee<sup>5</sup> found that among mice surviving for thirty-one days after inoculation with *Staphylococcus aureus*, cultures of organs were positive for the organism in 14 per cent of those animals treated with sulfathiazole, in 18 per cent of those treated with sulfapyridine, in 25 per cent of those treated with sulfamethylthiazole (2-[paraaminobenzenesulfonamido]-4-methylthiazole) and in 12.5 per cent of the untreated controls. One of the purposes of the present investigation was to study this angle of the problem, and, as will be shortly shown, a large percentage of our surviving mice and rabbits had macroscopic or microscopic abscesses in the kidneys.

Under the conditions nothing of proved or helpful value can be neglected in the treatment of staphylococcic septicemia of human beings, in addition to therapy with drugs of the sulfanilamide group. Unfortunately, the older so-called polyvalent antistaphylococcus serums have generally proved ineffective. However, since numerous investigators have shown that therapy with a drug of the sulfanilamide group and serum combined has proved more effective in the treatment of experimental streptococcic,<sup>6</sup> meningococcic<sup>7</sup> and pneumococcic<sup>8</sup> infections of mice than therapy with either agent alone, we thought it advisable to determine the effectiveness of chemoserotherapy in the treatment of staphylococcic infections of mice, employing the newer staphylococcus antitoxin, especially since the last-named substance has given encouraging results in the treatment of experimental staphylococcic infections,<sup>9</sup> as well as in the treatment of septicemia in human beings.<sup>10</sup> In other

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5. Rake, G., and McKee, C. M.: Action of Sulfathiazole and Sulfamethylthiazole on *Staphylococcus Aureus*, *Proc. Soc. Exper. Biol. & Med.* **43**:561, 1940.

6. Loewenthal, H.: Combined Serum and Sulfanilamide in the Treatment of Streptococcal Infections in Mice, *Lancet* **1**:197, 1939.

7. Branham, S. E., and Rosenthal, S. M.: Studies in Chemotherapy: Sulfanilamide, Serum, and Combined Drug and Serum Therapy in Experimental Meningococcus and Pneumococcus Infection in Mice, *Pub. Health Rep.* **52**:685, 1937.

8. MacLeod, C. M.: Chemotherapy of Pneumococcic Pneumonia, *J. A. M. A.* **113**:1405 (Oct. 7) 1939. Branham and Rosenthal.<sup>7</sup>

9. Burnet, F. M.: The Exotoxins of *Staphylococcus Pyogenes Aureus*, *J. Path. & Bact.* **32**:717, 1929. Parish, H. J.; O'Meara, R. A. J., and Clark, W. H. M.: The Clinical Investigation of Staphylococcal Toxin, Toxoid and Antitoxin, *Lancet* **1**:1054, 1934.

10. Panton, P. W.; Valentine, F. C. O., and Dix, V. W.: Staphylococcal Infection and Antitoxin Treatment, *Lancet* **2**:1180, 1931. Dolman, C. E.: Staphylococcus Antitoxic Serum in Treatment of Acute Staphylococcic Infections and Toxemia, *Canada. M. A. J.* **30**:601, 1934; **31**:1 and 130, 1934. Sutherland, R. T.: Staphylococcus Septicemia, *Arch. Int. Med.* **66**:1 (July) 1940.

words, there appears to be an important synergistic action between drugs of the sulfanilamide group and potent immune serums, and the results of our investigation reported here indicate that this action may be evinced in severe experimental staphylococcic infections.

#### MATERIAL AND METHOD

White mice were inoculated intravenously with 0.05 cc. of a highly virulent twenty-four hour broth culture of *Staph. aureus*. Of 120 untreated control animals, 18, or 15 per cent, survived twenty-one days. The kidneys of all treated and untreated mice, including those surviving this period, were examined macroscopically and microscopically for abscesses and the results recorded in tables 2 and 3.

Rabbits were given 0.1 cc. of eighteen hour broth cultures of the same strain intravenously once a day for eight days in succession in an effort to maintain a prolonged period of septicemia analogous to staphylococcic septicemia in human beings. Blood cultures made on the third, seventh, tenth and eighteenth days were positive for *Staph. aureus* in the majority of cases, and cultures made of the hearts of 15 animals immediately after death were all positive. The liver, kidneys, heart, etc., of all rabbits dying during treatment and those of all survivors were examined macroscopically and microscopically for abscesses; in table 4, 4 plus indicates the presence of numerous large and widely distributed abscesses, while 2 plus indicates the presence of microscopic abscesses only in the kidneys.

The shaved abdominal skin of additional rabbits was inoculated with 0.8 cc. of twenty-four hour broth culture of the staphylococcus. This dose was divided into four injections of 0.2 cc. each in a small area at the midline. Large lesions developed in about twenty-four hours, characterized by severe edema and hemorrhagic necrosis and similar to those produced by Kolmer and Rule<sup>11</sup> with hemolytic streptococcus and to those used by Kolmer, Brown, Rule and Werner<sup>12</sup> in a study of the therapeutic activity of sulfanilamide. In table 5, 4 indicates the presence of these large spreading lesions, due in most part to the presence of necrotizing toxin, while 3, 2 and 1 indicate lesions of progressively less severity. Cultures were made of material from the lesions, three, five, ten, fourteen and twenty-one days after inoculation and the results summarized in the table.

Azosulfamide (disodium of 4-sulfamidophenyl-2'-azo-7'-acetylamino-1'-hydroxynaphthalene-3',6'-disulfonate), sulfanilamide, sulfapyridine, sulfathiazole and the following new compounds<sup>13</sup> were employed in treatment:

Aldanil: sodium formaldehyde sulfoxylate derivative of sulfanilamide

No. 2344: diaminodiphenylsulfone

No. 2439: p-cinnamalamino-p'-amidodiphenylsulfone<sup>14</sup>

11. Kolmer, J. A., and Rule, A. M.: Experimental Streptococcus Infections in Rabbits for Therapeutic Investigations, *J. Lab. & Clin. Med.* **22**:1097, 1939.

12. Kolmer, J. A.; Brown, H.; Rule, A. M., and Werner, M. F.: Toxicity, Therapeutic Activity, and Mode of Action of Sulfanilamide in Experimental Streptococcus Infection of Rabbits, *J. Lab. & Clin. Med.* **24**:164, 1938.

13. These compounds were synthesized by Dr. George W. Raiziss, of the Dermatological Research Laboratories of the Abbott Laboratories, Inc., and supplied by him.

14. Raiziss, G. W.; Kolmer, J. A., and Rule, A. M.: Sulfone Compounds in the Treatment of Experimental Pneumococcal Infections, *J. Infect. Dis.* **66**:138, 1940.

- No. 2879: sulfathiazoline (sulfhydrothiazole; 2-sulfanilyl-3,5-dihydrothiazole)<sup>15</sup>  
No. 2898: tetramethyldecamethylenediamine-bis (4-chloracetamidophenyl)-sulfide polymeric quaternary salt  
No. 2946: 2-(paraaminobenzenesulfonamido)-pyrimidine  
No. 2949: acetaldehyde bisulfite derivative of sulfanilamide  
No. 2955: sulfadimethylpyrimidine

All of the compounds were administered to the mice orally in doses of 0.1 Gm. per kilogram of weight. The drug was first given four hours after inoculation and every twelve hours thereafter for a total of ten doses, equivalent to 0.2 Gm. per kilogram of weight daily. Four additional doses of 0.1 Gm. were then administered daily for four days in succession. In the case of surviving mice the total dose of each compound was therefore 2.4 Gm. per kilogram of weight over a period of fourteen to fifteen days.

Additional mice were treated in the same manner with azosulfamide, sulfanilamide, sulfapyridine and aldanil except that globulin-modified staphylococcus antitoxin<sup>16</sup> was given intra-abdominally in doses of 0.1 cc. (80 units) per mouse. The antitoxin was first injected four hours after inoculation and every twelve hours thereafter for a total of ten doses, followed by four additional doses at daily intervals.

In the treatment of the rabbits the compounds were administered orally or intramuscularly in doses of 0.1 Gm. per kilogram of weight, the first being given three days after inoculation in order to permit the septicemia to become well established. Subsequent doses were given every twelve hours for eight days, equivalent to 0.2 Gm. per kilogram of weight daily. In the treatment of intradermal lesions the compounds were given orally, subcutaneously or intravenously in doses of 0.1 Gm. per kilogram of body weight every twelve hours for five to twelve doses, with the first dose administered four hours after inoculation.

## RESULTS

*Chemotherapy of Staphylococcic Infections in Mice.*—The results observed with twelve compounds in the treatment of 316 mice are summarized in table 2. It will be observed that 14, or 15.5 per cent, of 90 additional untreated mice survived the period of observation of twenty-one days but all of these, as well as all mice which died, showed macroscopic or microscopic abscesses in the kidneys. The amount of culture employed therefore was about a single minimal lethal dose and thereby more favorable to the action of the compounds than an overwhelming infection would have been.

It will be observed that best results, from the standpoint both of survival and of escape from pyemic abscesses of the kidneys, were

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15. Raiziss, G. W., and Clemence, L. W.: 2-Sulfanilyl-aminothiazoline, J. Am. Chem. Soc. **63**:3124, 1941. Raiziss, G. W.; Severac, M., and Moetsch, J. C.: Chemotherapeutic Studies of 2-Sulfanilyl 3-5 Dihydrothiazole (Sulfathiazoline), to be published.

16. The antitoxin was supplied by Lederle Laboratories, Inc.

observed with sulfathiazole, sulfathiazoline and sulfapyridine, especially sulfathiazole and sulfathiazoline, which appear to be equal in therapeutic effectiveness, since the slight differences observed were easily within the range of experimental error. Next best results were observed with sulfadimethylpyrimidine (no. 2955), followed in order by the acetaldehyde bisulfite derivative of sulfanilamide (no. 2949), 2-(paraaminobenzenesulfonamido)-pyrimidine (no. 2946), sulfanilamide, aldanil, azosulfamide and tetramethyldecamethylenediamine-bis (4-chloracetamidophenyl)-sulfide polymeric quaternary salt (no. 2898), while diaminodiphenylsulfone

TABLE 2.—Results of Treatment of Mice Inoculated Intravenously with *Staph. Aureus*\*

Compound	No. of Doses †	No. of Mice	Survival, Days						Survival, %	Abscesses in Kidneys, %
			3	5	7	10	14	21		
Azosulfamide.....	14	24	18	16	16	14	8	8	33.3	91.7
Sulfanilamide.....	14	24	20	20	18	16	12	10	41.7	83.3
Sulfapyridine.....	14	52	50	47	40	38	31	27	51.9	50
Sulfathiazole.....	14	42	40	38	38	31	28	24	57.1	48
Sulfathiazoline.....	14	40	40	40	36	30	27	22	55	50
Aldanil.....	14	34	31	28	19	16	14	12	35.3	100
No. 2344 ‡.....	14	12	7	0	0	0	0	0	0	100
No. 2439 §.....	14	12	3	1	0	0	0	0	0	100
No. 2898   .....	14	12	12	10	6	4	4	4	33.3	66.6
No. 2946 ¶.....	14	14	14	12	12	10	8	6	42.8	71.4
No. 2949 #.....	14	20	20	15	12	11	10	9	45	69
No. 2955 **.....	14	30	26	26	24	23	18	15	50	80.6
Controls.....	..	90	73	60	35	22	14	14	15.5	100

\* The inoculum consisted of 0.05 cc. of a twenty-four hour broth culture.

† In doses of 0.1 Gm. per kilogram of weight the drugs were first given four hours after inoculation and were administered every twelve hours thereafter for a total of ten doses, followed by one dose daily for four successive days.

‡ Diaminodiphenylsulfone.

§ p-Cinnamalamino-p'-amidodiphenylsulfone.

|| Tetramethyldecamethylenediamine-bis (4-chloracetamidophenyl)-sulfide polymeric quaternary salt.

¶ 2-(paraaminobenzenesulfonamido)-pyrimidine.

# Acetaldehyde bisulfite derivative of sulfanilamide.

\*\* Sulfadimethylpyrimidine.

(no. 2344) and p-cinnamalamino-p'-amidodiphenylsulfone (no. 2439) were completely ineffective. It will also be noted that the incidence of abscesses in the kidneys showed a close relation to the therapeutic effectiveness of the compounds on the basis of percentage of survival.

*Chemotherapy of Staphylococcic Infections in Mice.*—The results observed in the treatment of 120 additional mice with six of the compounds alone and of 120 with the compounds combined with staphylococcus antitoxin are summarized in table 3. Of 30 untreated controls, 4, or 13.3 per cent, survived, although all 30 showed abscesses in the kidneys. Of 30 mice treated with the antitoxin alone, 10, or 33.3 per cent, survived and 66.6 per cent of the group showed abscesses in the



kidneys. The results have shown, therefore, that the staphylococcus antitoxin in the dose employed had definite therapeutic effects.

Sulfathiazole, sulfathiazoline and sulfapyridine alone again gave the best therapeutic results, followed in order by sulfanilamide, azosulfamide and aldanil. But it will be observed that combined treatment with one of the compounds and staphylococcus antitoxin gave better results from the standpoint both of percentage of survival and of incidence of abscesses in the kidneys than did therapy with any single compound. While staphylococcus antitoxin is administered to human beings primarily for

TABLE 3.—*Results of Chemotherapy of Mice Inoculated Intravenously with Staph. Aureus\**

Compound	Treatment			Survival, Days						Survival, %	Abscesses in Kidneys, %
	Doses Cpd.†	Anti-toxin‡	No. of Mice	3	5	7	10	14	21		
Azosulfamide.....	14	0	20	16	12	12	10	8	8	40	90
Azosulfamide.....	14	14	20	16	16	15	14	14	14	70	70
Sulfanilamide.....	14	0	20	18	18	16	16	8	8	40	80
Sulfanilamide.....	14	14	20	20	20	18	14	12	10	50	60
Sulfapyridine.....	14	0	20	18	18	16	14	12	10	50	60
Sulfapyridine.....	14	14	20	19	18	18	16	14	12	60	50
Sulfathiazole.....	14	0	20	20	20	18	16	13	12	60	50
Sulfathiazole.....	14	14	20	20	20	20	18	15	14	70	45
Sulfathiazoline.....	14	0	20	20	20	20	16	11	11	55	60
Sulfathiazoline.....	14	14	20	20	20	19	17	15	13	65	50
Aldanil.....	14	0	20	14	12	8	4	4	4	20	160
Aldanil.....	14	14	20	18	18	16	10	10	10	50	63
Antitoxin-treated controls.....	0	14	30	24	18	15	12	10	10	33.3	66.6
Untreated controls.....	0	0	30	24	16	12	7	4	4	13.3	100

\* The initial inoculum consisted of 0.05 cc. of a twenty-four hour broth culture.

† In doses of 0.1 Gm. per kilogram of weight the drugs were first given four hours after inoculation and were administered every twelve hours thereafter for a total of ten doses, followed by one dose daily for four successive days.

‡ Staphylococcus antitoxin was administered intra-abdominally in doses of 0.1 cc. per mouse. It was first given four hours after inoculation and was administered every twelve hours thereafter for a total of ten doses, followed by one dose daily for four successive days.

the relief of toxemia, it appears from the results of this experimental study to have a synergistic effect, with a distinct improvement in the therapeutic effectiveness of the drugs of the sulfanilamide group. For this reason we believe it is advisable to employ staphylococcus antitoxin in large doses, and preferably by intravenous administration, along with such drugs in the treatment of staphylococcic septicemia in human beings.

*Chemotherapy of Staphylococcic Infections in Rabbits.*—The first experiment consisted in the daily intravenous inoculation of 60 rabbits with 0.1 cc. of an eighteen hour broth culture of Staph. aureus for eight days, which produced septicemia in the majority of the animals. Treatment began on the third day, at which time blood cultures positive for the staphylococcus were obtained, a dose being given every twelve hours

for a total of sixteen doses over a period of eight days. In other words, the compounds were administered twice daily for five days along with a daily inoculation of staphylococci and were continued for three days after inoculation had been stopped.

As shown in table 4, 2 of the 6 untreated controls survived eighteen days, but these, as well as the 4 animals which died, showed numerous abscesses in the kidneys and other organs.

On the seventh day of treatment the blood of rabbits given sulfanilamide contained 1.2 to 6.8 mg. of free sulfanilamide per hundred cubic centimeters; that of those given azosulfamide orally contained 2.2 to

TABLE 4.—*Treatment of Rabbits Inoculated Intravenously with Staph. Aureus* \*

Compound	Administration †		No. of Rabbits	Survival, Days						Abscesses Evident at Necropsy ‡
	Dose, Gm. per Kg.	Route		3	5	7	10	14	18	
Sulfanilamide....	0.1	Oral	6	6	6	6	5	3	3	++++
Azosulfamide.....	0.1	Oral	6	6	5	4	3	3	3	++++
Azosulfamide.....	0.1	Intramuscular	6	6	5	5	4	3	3	++
Sulfapyridine....	0.1	Oral	6	6	6	6	6	4	4	++
Sulfathiazole..	0.1	Oral	6	6	6	6	6	5	5	++
Aldanil.....	0.1	Oral	6	6	6	6	5	4	2	++
Aldanil.....	0.1	Intramuscular	6	6	6	6	5	5	2	++
No. 2344 § ...	0.1	Oral	6	6	6	5	4	2	2	++++
No. 2439   .....	0.1	Oral	6	6	5	5	3	2	2	++++
Controls..	...	.....	6	6	5	3	3	2	2	++++

\* The inoculum consisted of 0.1 cc. of an eighteen hour broth culture daily for eight doses.

† The first dose was given on the third day, and the drug was administered every twelve hours for eight days.

‡ ++, microscopic abscesses only in the kidneys; +++, large and numerous abscesses in the kidneys, heart muscle, etc.

§ Diaminodiphenylsulfone.

|| P-cinnamalamino-p'-amidodiphenylsulfone.

3.2 mg. of drug, while that of animals given the latter compound intramuscularly contained 0.8 to 2.8 mg. The level of free drug in the blood of rabbits given sulfapyridine was 0.7 to 4.5 mg., per hundred cubic centimeters, while that in the blood of animals given sulfathiazole was 0.5 to 4.4 mg.

As shown in the table, best results were obtained with sulfathiazole and sulfapyridine; sulfathiazoline was not employed as it was not available at the time the experiment was conducted. It is possible that sulfanilamide and azosulfamide were slightly effective, but aldanil and compounds 2344 and 2439 had no demonstrable therapeutic effect.

The same seven compounds with the exception of sulfathiazole were used in the treatment of 27 rabbits inoculated intradermally with *Staph. aureus* in amounts of 0.1 Gm. per kilogram of weight. The first dose

was given four hours after intradermal inoculation, and the drug was administered every twelve hours thereafter for a total of twelve doses, except in the case of 1 animal which received a total of five doses and

TABLE 5.—*Treatment of Rabbits Inoculated Intracutaneously with Staph. Aureus\**

Compound	Administration †		Lesions, ‡ Days								Cultures of Material from Lesions, Days				
	Route	No. of Doses	1	2	3	5	7	14	21		3	5	10	14	21
Sulfanilamide ....	Oral	8	4	4	4	D	..	..	..	+	+	..	..	..	..
Sulfanilamide.....	Oral	12	4	3	3	2	2	1	—	+	+	+	—	—	—
Sulfanilamide.....	Oral	12	4	4	3	3	2	1	—	+	+	+	—	—	—
Sulfanilamide.....	Subcutaneous	12	4	4	4	4	2	—	—	+	+	+	+	—	—
Sulfanilamide ..	Subcutaneous	12	4	4	4	4	3	1	—	+	+	+	+	—	—
Sulfanilamide ..	Subcutaneous	12	4	4	4	3	3	—	—	+	+	+	+	—	—
Azosulfamide..	Oral	12	4	3	2	2	2	2	—	+	+	+	+	—	—
Azosulfamide..	Oral	12	4	3	3	2	2	2	—	+	+	+	+	—	—
Azosulfamide ..	Oral	12	4	4	3	2	1	—	—	+	+	+	—	—	—
Azosulfamide..	Subcutaneous	12	4	4	4	3	3	—	—	+	+	+	—	—	—
Azosulfamide..	Subcutaneous	12	4	4	4	3	2	—	—	+	+	+	—	—	—
Azosulfamide..	Subcutaneous	12	4	4	3	3	2	1	—	+	+	+	—	—	—
Sulfapyridine...	Oral	12	4	4	4	4	3	—	—	+	+	—	—	—	—
Sulfapyridine..	Oral	12	4	4	4	4	3	2	—	+	+	+	+	—	—
Sulfapyridine...	Oral	12	4	4	4	3	2	—	—	+	+	+	—	—	—
Sulfapyridine..	Intravenous	5	4	4	D	..	..	..	..	+	..	..	..	..	..
Sulfapyridine...	Intravenous	12	4	2	2	—	—	—	—	+	+	—	—	—	—
Sulfapyridine..	Intravenous	12	4	4	2	2	—	—	—	+	+	—	—	—	—
Aldanil....	Oral	12	4	4	3	2	2	2	—	+	+	—	—	—	—
Aldanil..	Oral	12	4	4	4	3	2	2	1	+	+	—	—	—	—
Aldanil...	Oral	12	4	4	3	2	2	2	—	+	+	—	—	—	—
No. 2344..	Oral	12	4	4	4	3	2	2	1	+	+	+	+	—	—
No. 2344 ..	Oral	12	4	4	4	3	1	D	..	+	+	..	..	..	..
No. 2344...	Oral	12	4	4	4	3	2	2	1	+	+	+	+	—	—
No. 2439..	Oral	12	4	4	4	3	2	2	1	+	+	+	+	—	—
No. 2439 ..	Oral	12	4	4	4	3	3	3	2	+	+	+	+	+	+
No. 2439 ..	Oral	12	4	4	4	3	2	2	2	+	+	+	+	—	—
Control..	.....	..	4	4	4	4	3	3	1	+	+	+	+	+	+
Control..	.....	..	4	4	4	4	3	1	—	+	+	+	—	—	—
Control...	.....	..	4	4	4	3	3	2	1	+	+	+	—	—	—

\* The inoculum consisted of 0.8 cc. of a twenty-four hour broth culture.

† In doses of 0.1 Gm. per kilogram of weight the drugs were first given four hours after inoculation and were administered every twelve hours thereafter.

‡ The following descriptive symbols are used: 4, large spreading lesions; 3, 2 and 1, local lesions of progressively less severity; —, absence of lesions, and D, death of animal.

1 which received eight doses. The routes of administration are shown in table 5.

Cultures were made of material from the lesions three, five, ten, fourteen and twenty-one days after inoculation, with the results shown in table 5. A determination of free sulfanilamide in the blood of the rabbits given this drug orally was made four hours after the fifth dose and showed 1.8 to 2.6 mg. per hundred cubic centimeters; similar levels

were observed in those rabbits given the compound subcutaneously. In the rabbits given azosulfamide orally the concentration of free drug was 0.5 to 0.8 mg. per hundred cubic centimeters, and in those given the drug by subcutaneous injection the level was 0.5 mg. In those given sulfapyridine orally the concentration was 0.5 to 1.0 mg. per hundred cubic centimeters, and in those receiving it intravenously the level was 0.8 mg.

All 3 untreated controls survived but showed severe local lesions, with cultures positive for the staphylococcus during the first seven days after inoculation. That 2 recovered spontaneously was indicated by cultures made from material taken from the lesions on the twenty-first day which remained negative for the causative organism.

Of the 27 treated animals, 3 died during the period of observation, with cultures of material taken from a lesion which were positive for the staphylococcus. Cultures of heart blood from these rabbits made immediately after death were positive for the staphylococcus.

It is difficult, however, to draw any deductions from the results except that sulfapyridine was apparently the most effective of the six compounds. Sulfathiazole and sulfathiazoline were not employed, as they were not available at the time the experiment was conducted. Aldanil and compounds 2344 and 2439 were ineffective, while sulfanilamide and azosulfamide yielded doubtful results.

#### SUMMARY

Sulfathiazole and sulfathiazoline have proved most effective in the treatment of experimental *Staph. aureus* infections in mice. Sulfapyridine ranked third and sulfadimethylpyrimidine fourth in therapeutic effectiveness.

The complete cure of mice, however, is not indicated by the survival rates, as varying percentages of mice surviving twenty-one days have shown the presence of pyemic abscesses in the kidneys. There is, however, a relation between the percentage of survival and the incidence of renal abscesses.

The simultaneous administration of staphylococcus antitoxin and drugs of the sulfanilamide group (chemosotherapy) has given somewhat better therapeutic results than therapy with the latter agents alone in the treatment of mice inoculated with *Staph. aureus*.

Sulfathiazole and sulfapyridine also proved most effective of the compounds used in the treatment of staphylococcic septicemia in rabbits. Sulfathiazoline was not employed. All of the animals surviving eighteen days, however, showed the presence of pyemic abscesses in the kidneys or other organs, so that survival alone is not an index of complete cure.

Sulfapyridine was also somewhat effective in the treatment of local lesions produced by the intradermal inoculation of *Staph. aureus*. Sulfathiazole and sulfathiazoline were not employed.

Two sulfone compounds were ineffective in the treatment of experimental staphylococcic infections in mice and rabbits.

The results have indicated, therefore, that sulfathiazole, sulfathiazoline and sulfapyridine possess therapeutic activity against experimental staphylococcic infections but frequently fail to bring about complete recovery insofar as pyemic abscesses of the kidneys and other internal organs are concerned. Under the circumstances, it is concluded that the chemotherapy of staphylococcic infections is still unsatisfactory and certainly inferior to therapy with the drugs of the sulfanilamide group in hemolytic streptococcic and pneumococcic infections.

# QUANTITATIVE STUDIES ON ANTITHROMBIN

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The failure of the circulating blood to clot spontaneously under physiologic conditions in vivo still remains a unique and obscure phenomenon, since all of the elements essential for immediate coagulation in vitro are apparently present. Howell, in his fundamental concept of blood coagulation, has consistently maintained in at least partial explanation of this enigma that substances acting as clotting inhibitors are normally present in blood plasma. With the identification of heparin by Howell and Holt<sup>1</sup> and the demonstration of the presence of proantithrombin, the nature and role of these anticoagulants in the blood began to be better understood. Evidence has been presented suggesting that the principal anticoagulant effect of heparin is the prevention of the conversion of prothrombin to thrombin. However, when added to plasma, heparin apparently activates the proantithrombin, resulting in a tremendous increase in antithrombic activity. Charles and Scott,<sup>2</sup> among others, have confirmed the presence of heparin in blood and isolated 185 units of crude heparin from 1 Kg. of ox plasma and a negligible amount from ox serum. Jerpes, Holmgren and Wilander<sup>3</sup> have recently suggested that the site of formation of heparin is in the mast cells of Ehrlich. Thus these cells, which are widespread throughout the body tissues, may constitute a "secretory organ" the function of which is to maintain the fluid character of the blood in vivo.

The normally existing anticoagulants, or clotting inhibitors, in blood serum and plasma, according to the present concepts, are antiprothrom-

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1. (a) Howell, W. H., and Holt, E.: Two New Factors in Blood Coagulation: Heparin and Pro-Antithrombin, *Am. J. Physiol.* **47**:328-341, 1918. (b) Howell, W. H.: The Purification of Heparin and Its Presence in Blood, *ibid.* **71**:553-562, 1925.

2. Charles, A. F., and Scott, D. A.: Studies in Heparin: II. Heparin in Various Tissues, *J. Biol. Chem.* **102**:431-435, 1933.

3. Jerpes, E.: On Heparin: Its Chemical Nature and Properties, *Acta med. Scandinav.* **88**:427-433, 1936. Holmgren, H., and Wilander, O.: Beitrag zur Kenntnis der Chemie und Funktion der Ehrlichschen Mastzellen, *Ztschr. f. mikr.-anat. Forsch.* **42**:242-278, 1937. Wilander, O.: Studien über Heparin, *Skandinav. Arch. f. Physiol. (supp. 15)* **81**:1, 1938.

bin, antithromboplastin and antithrombin (fig. 1). Antiprothrombin prevents the conversion of prothrombin to thrombin. There is some doubt as to the exact nature of antiprothrombin, the accumulated evidence suggesting that the prevention of the conversion of prothrombin to thrombin is due to an antithromboplastic action. Brinkhous, Smith, Warner and Seegers<sup>4</sup> have shown that heparin requires an additional plasma factor before it can prevent the formation of thrombin and have postulated that the anticoagulant effect may be due to an antithromboplastic rather than an antiprothrombic effect. Ferguson<sup>5</sup> expressed a preference for the view that the antiprothrombic effect of heparin is to be interpreted not as an alteration in prothrombin itself but rather as a manifestation of antagonisms between heparin and thromboplastic factors. Howell<sup>6</sup> has stated on numerous occasions that thromboplastin will neutralize the effect of heparin and has postulated that thromboplastin combines with the antiprothrombin of the antiprothrombin-prothrombin combination, resulting in the release of free prothrombin. Sterner and

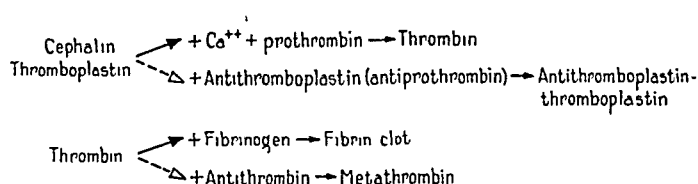


Fig. 1.—The sequence of events in blood coagulation, illustrating the possible fate of cephalin, thromboplastin and thrombin.

Medes<sup>7</sup> have shown that cysteine and other cystine derivatives have an antiprothrombic action.

The plasma of normal human subjects contains 300 units of prothrombin per cubic centimeter, 1 unit being defined as that amount which when converted to thrombin will clot 1 cc. of fibrinogen in fifteen seconds.<sup>8</sup> Thus plasma contains sufficient potential thrombin in the

4. Brinkhous, K. M.; Smith, H. P.; Warner, E. D., and Seegers, W. H.: The Inhibition of Blood Clotting: An Unidentified Substance Which Acts in Conjunction with Heparin to Prevent the Conversion of Prothrombin into Thrombin, *Am. J. Physiol.* **125**:683-687, 1939.

5. Ferguson, J. H.: Heparin and Plasma Albumin in Relation to Thromboplastic Action of Trypsin, Cephalin and Brain Extracts, *Proc. Soc. Exper. Biol. & Med.* **42**:33-37, 1939.

6. (a) Howell, W. H.: Theories of Blood Coagulation, *Physiol. Rev.* **15**:435-470, 1935. (b) Footnote 1.

7. Sterner, J. H., and Medes, C.: The Effect of Certain Sulfur Compounds on the Coagulation of Blood, *Am. J. Physiol.* **117**:92-101, 1936.

8. Smith, H. P.: Prothrombin and Thrombin, read at the meeting of the American Association for the Advancement of Science, Columbus, Ohio, Dec. 27, 1939.

form of its precursor prothrombin to clot 300 cc. of fibrinogen in fifteen seconds. When normal blood is allowed to clot the thrombin is almost entirely inactivated or neutralized in one or two hours. Brinkhous, Smith and Warner<sup>9</sup> have shown that hemorrhage may occur when the prothrombin level is below 35 per cent of normal, i. e., below 105 units per cubic centimeter. Persons with this degree of hypoprothrombinemia have sufficient potential thrombin in the form of the precursor prothrombin to clot 105 cc. of fibrinogen in fifteen seconds. The occurrence of hemorrhage is only partially explained on the basis of decreased levels and the convertibility of plasma prothrombin. From these observations it is quite evident that the thrombin must be inactivated or neutralized in such proportions that a hemorrhagic tendency develops. However, an analysis of the available methods for the quantitative determination of antithrombin would indicate that serum or plasma can inactivate only a fraction of a unit of thrombin in ten to fifteen minutes. Howell<sup>6a</sup> has stated that blood contains but a small amount of thrombin. Therefore it is obvious that either the antithrombic activity is much greater than measured by previous methods or the thrombin is neutralized or inactivated in some other manner.

Quantitative determinations of antithrombin in blood serum and plasma have not been entirely satisfactory up to the present time because of the lack of quantitative data relating to the various other essential elements in the blood-clotting mechanism. The various methods which, from time to time, have been suggested for the determination of antithrombin and of other anticoagulants have given only qualitative or crude quantitative estimations. Howell<sup>10</sup> and Gasser<sup>11</sup> observed the antithrombic activity of serum which had been heated to remove all traces of thrombin and fibrinogen. Thrombin was then added and after suitable periods of incubation the ability of the mixture to coagulate fibrinogen was determined. Mills and Kitzmiller<sup>12</sup> used a similar method in studying the antithrombin of blood serum from patients with typhoid fever; their data showed an increase. Quick<sup>13</sup> and Eagle, Johnston and

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9. Brinkhous, K. M.; Smith, H. P., and Warner, E. D.: Prothrombin Deficiency and the Bleeding Tendency in Obstructive Jaundice and in Biliary Fistula, *Am. J. M. Sc.* **196**:50-57, 1938.

10. Howell, W. H.: The Condition of Blood in Hemophilia, Thrombosis and Purpura, *Arch. Int. Med.* **13**:76-95 (Jan.) 1914.

11. Gasser, W. H.: The Significance of Prothrombin and of Free and Combined Thrombin in Blood-Serum, *Am. J. Physiol.* **42**:378-394, 1916.

12. (a) Mills, C. A., and Kitzmiller, K. V.: Aid in Diagnosis of Typhoid Fever: New Laboratory Method, *Arch. Int. Med.* **38**:544-550 (Oct.) 1926. (b) Mills, C. A.: Antithrombin Test in Typhoid Fever: Improvement in Technic, *ibid.* **39**:618-620 (May) 1927.

13. Quick, A. J.: The Normal Antithrombin of the Blood and Its Relation to Heparin, *Am. J. Physiol.* **123**:712-719, 1938.



Ravdin<sup>14</sup> added various amounts of thrombin to plasma and observed the variations in coagulation time. These investigators used their methods for determining experimental increases in antithrombin and apparently never intended them to be used for observations on normal plasma. The method of Chargaff, Bancroft and Stanley-Brown,<sup>15</sup> in which an inhibitor unit is defined, is not well adapted to the study of antithrombin, as both the antiprothrombin and the antithrombin must be observed in one step. Heparin units, as defined by Howell,<sup>16</sup> cannot be readily converted into corresponding quantities of antithrombin per se.

With the recent development of a technic for the standardization and purification of thrombin by Warner, Brinkhous, Smith and Seegers,<sup>17</sup> it has become possible to devise an adequate method for the quantitative determination of antithrombin.<sup>18</sup> It must be obvious that any method for the determination of antithrombin involves the principle of the inactivation of thrombin. Before such a method could be devised, however, various quantitative observations were necessary on the inactivation of thrombin by potassium oxalate, blood plasma and serum. The disappearance of thrombin during the conversion of fibrinogen to fibrin was measured quantitatively. Observations were then made on the inactivation of thrombin by diluted and undiluted serum and plasma. With these data a dependable test has been devised for the quantitative determination of antithrombin. The normal levels of antithrombin were then determined in normal human subjects and in various laboratory and domestic animals.

#### METHOD

The prothrombin-free fibrinogen was prepared by the method of Warner, Brinkhous and Smith,<sup>17b</sup> all procedures being carried out at 5 C. and the materials stored at -35 C. The thrombin was prepared by the method of Seegers, Brinkhous, Smith

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14. Eagle, H.; Johnston, C. C., and Ravdin, I. S.: On the Prolonged Coagulation Time Subsequent to Anaphylactic Shock, *Bull. Johns Hopkins Hosp.* **60**:428-438, 1937.

15. Chargaff, E.; Bancroft, F. W., and Stanley-Brown, M.: Studies on the Chemistry of Blood Coagulation: The Measurement of the Inhibition of Blood Clotting; Methods and Units, *J. Biol. Chem.* **115**:149-154, 1936.

16. Howell, W. H.: Heparin, an Anticoagulant, *Am. J. Physiol.* **63**:434-435, 1922.

17. (a) Warner, E. D.; Brinkhous, K. M., and Smith, H. P.: The Titration of Prothrombin in Certain Plasmas, *Arch. Path.* **18**:587 (Oct.) 1934; (b) Quantitative Study on Blood Clotting: Prothrombin Fluctuations Under Experimental Conditions, *Am. J. Physiol.* **114**:667-675, 1936. (c) Smith, H. P.; Warner, E. D., and Brinkhous, K. M.: Prothrombin Deficiency and the Bleeding Tendency in Liver Injury (Chloroform Intoxication), *J. Exper. Med.* **66**:801-811, 1937. (d) Seegers, W. H.; Brinkhous, K. M.; Smith, H. P., and Warner, E. D.: The Purification of Thrombin, *J. Biol. Chem.* **126**:91-95, 1938.

18. Wilson, S. J.: Quantitative Studies on Antithrombin, *Proc. Soc. Exper. Biol. & Med.* **43**:676-678, 1940.

and Warner and standardized by either the pipet or the dropper method. The standardization tests should be repeated just before any critical observations are made.

The following method was devised to determine accurately fractions of 1 unit of thrombin: Fifteen drops of physiologic solution of sodium chloride was added to each of 9 test tubes. A series of 9 dilutions containing 0.2 to 1.0 unit of thrombin in each drop was then prepared, and portions of a single drop were added in sequence to the tubes of saline solution. To each test tube was then added 5 drops of fibrinogen (a total of 21 drops), and the appearance of the fibrin strands was timed with a stopwatch. The following clotting times were observed:

Units of Thrombin	Clotting Time, Sec.
1.0	20
0.9	21.5
0.8	23.5
0.7	25.5
0.6	27.5
0.5	31
0.4	35.5
0.3	40.5
0.2	46.5

A curve to be used in the studies on quantitative antithrombic activity was then plotted. One unit of thrombin was used in the studies. If the figures for the thrombin are reversed the curve will indicate the amount of thrombin inactivated or neutralized.

#### QUANTITATIVE ANTITHROMBIC ACTIVITY OF SERUM AND PLASMA

Blood was obtained from a rabbit by heart puncture, and a portion was mixed with one seventh of its volume of a 1.85 per cent solution of potassium oxalate. The serum and plasma were removed after centrifugation. Portions of the serum and plasma were incubated at 63 C. for ten minutes and the precipitated fibrinogen of the plasma discarded. A part of the incubated plasma was placed in a cellulose membrane and dialyzed against cold distilled water until the potassium oxalate and other electrolytes were removed, this point being easily determined by the precipitation of the water-insoluble euglobulin fraction.

Dilutions of the plain serum, the incubated serum and the plain and the dialyzed incubated oxalated plasma of 1:65 were prepared with physiologic solution of sodium chloride and corrections made for dilution by the oxalate solution or increase in volume by dialysis. A series of test tubes was set up for each specimen with 15 drops of serum or plasma in each tube. One unit (1 drop) of thrombin was added to each tube and incubated at 28 C. for various intervals, after which 5 drops of fibrinogen was added. The clotting times were observed and the amount of thrombin inactivated was determined. There was but a negligible difference in the antithrombic activity in the various prepa-

rations, all variations being within the range of experimental error (fig. 2). Potassium oxalate will inactivate thrombin, this effect apparently being lost in dilutions as great as were used in these observations. The blood should not be mixed with greater than one seventh of its volume of a 1.85 per cent solution of potassium oxalate. This substance does not activate the proantithrombin of the plasma as does heparin. Dialysis with the cellulose membrane did not result in a decrease in the ability of the plasma to inactivate thrombin.

The antithrombic activity of undiluted serum and plasma was then determined (table 1). The following specimens were prepared from rabbit's blood: serum, serum incubated at 56 C. for ten minutes, oxalated plasma (2.8 mg. of potassium oxalate per cubic centimeter) incubated at 56 C. for ten minutes to precipitate and remove the fibrinogen and

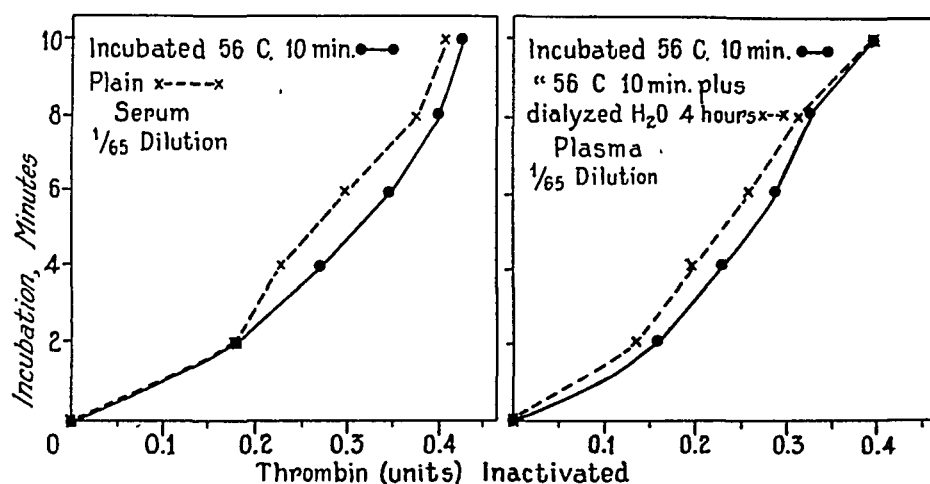


Fig. 2.—The quantitative antithrombic activity of saline dilutions of serum, incubated serum, incubated plasma and dialyzed incubated plasma in a physiologic solution of sodium chloride. The curves of activity are essentially the same.

TABLE 1.—*Inactivation of Thrombin by Undiluted Serum and Plasma (Rabbit)*

Specimen	Units of Thrombin Added per Cc.	Units of Thrombin Inactivated in 4 Minutes
Serum, plain .....	140	126
Serum, incubated 10 min. at 56 C. ....	140	124
Plasma, oxalated, fibrinogen removed by incubating for 10 min. at 56 C. ....	140	132
Plasma, oxalated, fibrinogen removed by adding 3 units of thrombin per cubic centimeter and removing fibrin clot .....	140	133

plasma from which the fibrinogen had been removed after having been converted to fibrin by the addition of 3 units of thrombin per cubic centimeter. To 1 cc. of each specimen was added 140 units of thrombin (0.1 cc.) and the amount calculated that was inactivated in four minutes'

incubation at 28 C. The amount of thrombin inactivated by the potassium oxalate was less than 0.1 unit; so no correction was necessary. Although plasma appeared to have a greater amount of antithrombic activity than serum, the difference was less than 6 per cent, a variation well within the present range of experimental error. Further detailed investigation is necessary to establish whether such relatively minor variations are constant and of any significance.

#### DISAPPEARANCE OF THROMBIN FROM SOLUTION DURING THE CONVERSION OF FIBRINOGEN TO FIBRIN

A prothrombin-free solution of fibrinogen was prepared, with a physiologic solution of sodium chloride used as the diluent. Oxalated

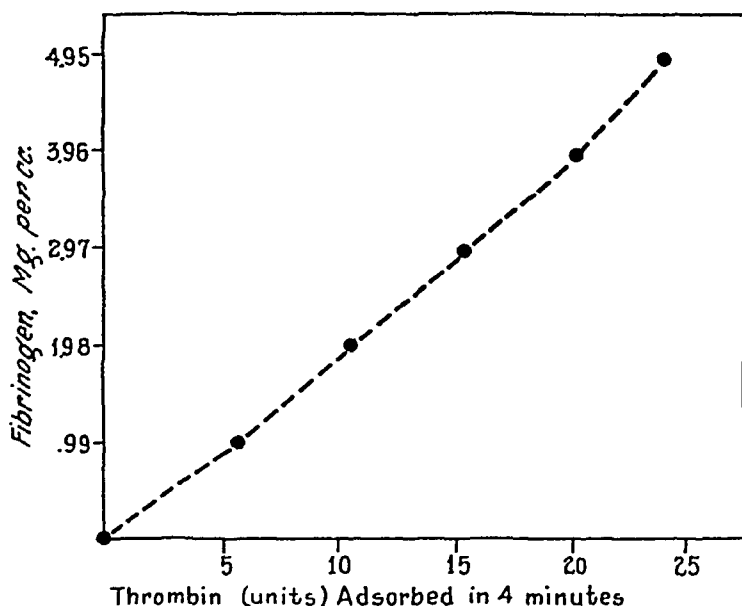


Fig. 3.—The adsorption of thrombin by various quantities of fibrinogen when converted to fibrin. Each milligram of fibrin adsorbed 5.1 units of thrombin.

saline solutions of fibrinogen were not used because of the thrombin-neutralizing power of potassium oxalate. The fibrinogen concentration was 4.95 mg. per cubic centimeter, as measured by the method of Greenberg and Mirolubova.<sup>19</sup>

Quantitative observations were then made on the amount of thrombin adsorbed by the conversion of varying amounts of fibrinogen to fibrin (fig. 3). A series of dilutions of various concentrations of fibrinogen was prepared. To 1 cc. of each dilution was added 35 units of thrombin, which resulted in the rapid and complete conversion of fibrinogen to

19. Greenberg, D. M., and Mirolubova, T. N.: Modifications in the Colorimetric Determinations of the Plasma Proteins by the Folin Phenol Reagent, *J. Lab. & Clin. Med.* **21**:431-435, 1936.

fibrin within a few seconds. The fibrin clot was removed from each tube after four minutes' incubation at 28 C. and the amount of thrombin accurately determined in the remaining liquid medium. From these data the quantity of thrombin which had disappeared from solution was calculated. When the curve was plotted the amount of thrombin utilized or adsorbed on the fibrin strands was shown to be in direct proportion to the concentration of the fibrinogen. Thus, the conversion of 1 mg. of fibrinogen to fibrin caused the disappearance of an average of 5.1 units of thrombin.

The question next to be decided was whether the fibrinogen when converted to fibrin in the presence of rather high concentrations of thrombin adsorbed its maximum amount of thrombin in four minutes or whether the adsorption process continued with longer periods of incubation. A series of 7 test tubes was prepared, each containing 1 cc. of fibrinogen (4.95 mg.). To each tube was added 55 units of thrombin. After various suitable periods of incubation, ranging from one to twenty-four minutes at 28 C., there was no variation in the amount of adsorbed thrombin calculated when the fibrin clot was removed. Apparently the saturation point of the adsorption of thrombin on the fibrin strands is quickly reached when the conversion of fibrinogen to fibrin occurs in the presence of excess amounts of thrombin.

#### ANTITHROMBIC ACTIVITY OF DILUTED AND UNDILUTED SERUM AND PLASMA

Rabbit plasma was incubated at 56 C. for ten minutes and the precipitated fibrinogen removed by centrifugation. Dilutions of the plasma of 1:10, 1:20, 1:30, 1:40, 1:50 and 1:60 were prepared with physiologic solution of sodium chloride, and the antithrombic activity of each was recorded for various periods of incubation at 28 C. After plotting the curves of each dilution, it was noted that there was a definite quantitative correlation at the end of four minutes' incubation in dilutions greater than 1:40. Subsequent observations on serum confirmed this observation. Theoretically, therefore, if 1 cc. of a 1:50 dilution of plasma or serum inactivates or neutralizes 0.5 unit of thrombin in four minutes, undiluted plasma or serum should inactivate or neutralize fifty times as much, or 25 units. It was obvious from the amount of thrombin inactivated by serum and plasma in the previous studies that the antithrombic activity of diluted plasma is not a true index of the ability of undiluted plasma or serum to neutralize thrombin.

The following observations were made in an attempt to correlate the thrombin-neutralizing activity of diluted and undiluted serum and plasma (table 2). Such a correlation was advisable because of the technical difficulties in preparing purified thrombin in quantity. The antithrombic

activity of 10 specimens of diluted serum which had been incubated at 56 C. for ten minutes was determined, only those dilutions being used in which sufficient thrombin remained after four minutes of incubation at 28 C. to clot the added fibrinogen in thirty to thirty-five seconds. The calculated amounts of thrombin inactivated were between 15.5 and 27.0 units per cubic centimeter of serum. Various quantities of purified thrombin were then added to 1 cc. of each specimen of undiluted serum and the amounts determined that were neutralized in four minutes' incubation at 28 C. Regardless of the quantity of thrombin added, there was always a small amount remaining. Thus, the addition of small amounts (15 to 60 units) of thrombin did not give a true index of the antithrombic activity. Because of these findings, 100 to 140 units of thrombin was added to each cubic centimeter of the undiluted serum, and

TABLE 2.—*Variations in the Antithrombic Activity of Diluted and Undiluted Serum, with Calculation of the Average Correction Factor*

Source	Units of Thrombin Added per Cc.	Units of Thrombin Inactivated in 4 Minutes	Calculated Units of Thrombin Inactivated per Cc., Dilution Method	Correction Factor *
Normal human subject . . . . .	100	86.0	16.5	5.21
Normal human subject . . . . .	100	89.0	15.5	5.74
Normal human subject . . . . .	100	88.0	16.5	5.33
Normal human subject . . . . .	120	101.0	20.0	5.05
Rabbit . . . . .	100	87.5	16.5	5.30
Rabbit . . . . .	100	87.0	16.5	5.27
Rabbit . . . . .	100	89.0	16.5	5.27
Rabbit . . . . .	120	107.0	20.0	5.39
Rat (albino) . . . . .	140	133.0	27.0	4.92
Rat (albino) . . . . .	140	122.0	23.0	5.30

\* The average correction factor was 5.28.

it was observed that from 86 to 133 units was inactivated in four minutes. Hence, to correlate the antithrombin of diluted and undiluted serum a correction factor of 5.28 was necessary, which was obtained by dividing the amount of thrombin neutralized by undiluted serum by the amount of thrombin calculated to be inactivated by the diluted serum.

#### METHOD FOR THE QUANTITATIVE DETERMINATION OF ANTI-THROMBIN IN SERUM AND PLASMA

With these accumulated data from the studies on quantitative activity of antithrombin it has been possible to devise a test for the titration of antithrombin in serum and plasma.

Venous blood is obtained and either is allowed to clot or is mixed with one seventh of its volume of a 1.85 per cent solution of potassium oxalate. After centrifugation the hematocrit reading and the total volume of the oxalate blood are carefully recorded to permit correction for dilution by the oxalate. The plasma or serum is collected after centrifugation and incubated in a water bath for ten

minutes at 56 C. The precipitated fibrinogen of the plasma may then be removed by centrifugation. Serum does not require centrifugation. Dilutions of the serum or plasma of 1:40, 1:50 and 1:60 are made with physiologic solution of sodium chloride. To 15 drops of each dilution is added 1 drop of thrombin containing 1 unit. The mixture is then allowed to stand for four minutes before the addition of 5 drops of fibrinogen. The time of the appearance of the fibrin strands is then determined. The end point is quite distinct. The incubation temperature should be 28 to 30 C. For accurate readings only those dilutions in which the clotting time occurs between twenty-eight and thirty-five seconds are used.

On the basis of observed quantitative activity, 1 unit of antithrombin is defined as that amount which will inactivate 1 unit of thrombin in four minutes at 28 C. No variation in antithrombic unitage occurs between 25 and 37 C. if the thrombin is standardized at the same temperature utilized in the ultimate test. In calculating the number of units per cubic centimeter of plasma, correction is made for the oxalate dilution factor. No such correction is necessary for the serum. The denominator of the final dilution is then multiplied by the amount of thrombin

TABLE 3.—*Normal Levels of Antithrombin in the Blood of Human Subjects and Various Animals*

Source	Number of Subjects	Average Antithrombin, Units per Cc.	Range of Variation, Units per Cc.*
Normal human subject . . . . .	34	90	74-115
Dog . . . . .	15	87	74-105
Cat. . . . .	5	96	79-117
Cow . . . . .	11	93	82-119
Pig..... .	4	103	101-109
Guinea pig . . . . .	10	108	97-120
Rabbit... .	18	108	98-133
Rat (albino) ... . . . .	28	123	102-147

\* Lowest and highest determinations.

inactivated and the result multiplied by the correction factor, 5.28. The answer obtained is in units of antithrombin per cubic centimeter of serum or plasma.

#### LEVELS OF ANTITHROMBIN IN BLOOD SERUM AND PLASMA

Blood was obtained from human subjects and various laboratory and domestic animals and the antithrombin of the serum or plasma determined by the method just described. In those cases in which the antithrombin was determined on both serum and plasma, the slight variations noted were within the range of experimental error.

The antithrombin level of the individual species was fairly constant. Human subjects have an average antithrombin level of 90 units per cubic centimeter. Dogs, cats and cattle have approximately the same antithrombin levels as human beings. The antithrombin level of guinea pigs, hogs and rabbits is slightly higher. The highest average unitage observed in the species studied was 123 units in the albino rat. It was interesting to note that calves consistently had slightly more antithrombin than cattle.

Daily observations were made on 1 normal human subject and a small series of dogs and rabbits. The antithrombin level of each subject was found to remain remarkably constant from day to day, variations of only  $\pm 5$  per cent having been recorded. All specimens of blood were obtained when the subject was in the fasting state, and no attempt was made to study the possible effect of various dietary measures.

The antithrombin and prothrombin concentrations were observed in a person with severe cirrhosis of the liver accompanied by spontaneous ecchymosis and bleeding gums. The plasma prothrombin was 25 per cent of normal, or 75 units per cubic centimeter, and the antithrombin was 95 units. In another patient with obstructive jaundice due to carcinoma of the head of the pancreas but with no clinical evidence of hemorrhage the prothrombin was 29 per cent of normal, or 87 units per cubic centimeter, and the antithrombin was 90 units per cubic centimeter. It is perhaps worthy of note that the hemorrhagic zone in hypoprothrombinemia occurs at the level at which the prothrombin unitage approximates or is lower than the antithrombin unitage.

#### COMMENT

There is little, if any, difference in the antithrombic activity of serum and plasma. This is surprising when one realizes that the antithrombin of rabbit serum has already inactivated from 270 to 300 units of thrombin. From these observations it seems justified to conclude that the normal antithrombin of blood is quantitatively altered little, if any, during the clotting process. Charles and Scott,<sup>2</sup> however, were able to obtain only a trace of heparin from serum, although they observed that plasma contained 185 units in crude form.

The exact chemical nature of antithrombin as it exists in normal serum and plasma is not known. Howell and Holt<sup>1</sup> have demonstrated both antithrombin and heparin in plasma. Landsberg<sup>20</sup> postulated that thrombin is probably adsorbed by serum proteins, just as rennin may be adsorbed by casein. Quick,<sup>18</sup> in a recent review of the subject, cited evidence for the identity of normal antithrombin of blood with serum albumin or with a closely related substance. The addition of heparin to albumin increases the ability of the latter to neutralize or inactivate thrombin. These observations have been confirmed by Ferguson.<sup>5</sup> Ziff and Chargaff<sup>21</sup> stated that the antithrombin is present in the more soluble portion of the albumin fraction. The ability of serum or plasma

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20. Landsberg, M.: Studien zur Lehre von der blutgerinnung. Physikalisch-chemische Vorgänge in ihrer Bedeutung für die Thrombinwirkung, *Biochem. Ztschr.* **50**:245, 1913.

21. Ziff, M., and Chargaff, E.: The Mechanism of Action of Heparin, *Proc. Soc. Exper. Biol. & Med.* **43**:740-742, 1940.



to inactivate thrombin is destroyed by incubation for ten minutes at 66 to 67 C. The importance of the  $\text{SO}_3\text{H}$  group has been emphasized by Demole and Reinert.<sup>22</sup> Howell<sup>23</sup> reported that heparin is a complex compound containing uronic acids, calcium and sulfuric acids. Jorpes<sup>24</sup> has stated that chemically heparin is probably a polysulfuric ester of mucoitin. Chargaff, Bancroft and Stanley-Brown<sup>25</sup> have noted that all substances of high molecular weight active in the inhibition of blood clotting contain sulfur. The antithrombin of serum or plasma, as is probably true of antiprothrombin, requires the presence of two factors, an activator, such as heparin, and the precursor of antithrombin, designated by Howell as proantithrombin.

The effect of electrolytes on the coagulation of fibrinogen by thrombin has been reported by Glasko and Greenberg.<sup>26</sup> Anions inhibit coagulation by acting directly on thrombin, the antithrombic action being negligible for univalent ions and increasing strongly with the valency. The inhibiting action of polyvalent cations is due to an effect on the fibrinogen. Although potassium oxalate will inactivate thrombin, the mechanism invoked is entirely different from that affecting heparin. Howell and Holt<sup>1</sup> have shown that heparin activates the proantithrombin of plasma, resulting in a marked increase in antithrombin, but heparin has a weak antithrombic activity per se. That potassium oxalate does not activate proantithrombin has been demonstrated in these studies by the fact that in high dilutions there is no difference in the activity of antithrombin of oxalated plasma and that of plasma which has had the oxalate removed by dialysis. Although not reported in detail, experimental observations on the addition of heparin to plasma indicated a marked increase in antithrombin.

During the actual process of blood coagulation the prothrombin is converted to thrombin. Thrombin has two possible fates; either it may combine with the fibrinogen, which results in the production of fibrin, or it may be inactivated or neutralized by antithrombin, with the sub-

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sequent formation of metathrombin. Mellanby<sup>27</sup> and Stromberg<sup>28</sup> have shown that when fibrinogen and thrombin are mixed together there is no decrease in the free thrombin until the very moment of coagulation, at which time a large portion suddenly disappears from the fluid. Gessard,<sup>29</sup> Foà<sup>30</sup> and Eagle<sup>31</sup> suggested that the thrombin is carried down with the clot, perhaps adsorbed onto its fibrils. Howell<sup>32</sup> has recovered thrombin from dried fibrin. Because of the lack of standardization of the various individual coagulation factors, no absolute quantitative studies were possible until the observations of Smith and his co-workers became available. The present observations have revealed that 1 mg. of fibrinogen causes the disappearance of 5.1 units of thrombin from solution. When fibrinogen is converted to fibrin in the presence of an excess of thrombin, the saturation point is rapidly reached in less than one minute and no further adsorption of thrombin occurs. Human plasma normally contains 2.2 to 4.5 mg. of fibrinogen per cubic centimeter. Thus, if plasma contains 300 units of potential thrombin in the form of its precursor prothrombin, only 11 to 22.5 units is adsorbed during the conversion of fibrinogen to fibrin, the remaining 277.5 to 289 units being neutralized or inactivated by the antithrombin.

With the data obtained in these observations, it has been possible to devise an adequate method for the quantitation of antithrombin. One cubic centimeter of human plasma or serum will inactivate or neutralize from 74 to 115 units of thrombin in four minutes by this method. Before the results of the present technic can be compared with those of procedures previously utilized an analysis of the methods is advisable. Such a comparison has only been possible since the purification and standardization of prothrombin and thrombin.<sup>17</sup> The methods previously used for the quantitative determinations of antithrombin have consisted of either adding less than 1 unit of thrombin to undiluted serum and observing the clotting time on the addition of fibrinogen after various periods of incubation<sup>33</sup> or adding a fraction of a unit or a few units to

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27. Mellanby, J.: The Rate of Fibrin Ferment from Prothrombin by the Action of Thrombokinase and Calcium Chloride, *J. Physiol.* **51**:396-403, 1917.

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31. Eagle, H.: Studies on Blood Coagulation: II. The Formation of Fibrin from Thrombin and Fibrinogen, *J. Gen. Physiol.* **18**:547-555, 1935.

32. Howell, W. H.: The Preparation and Properties of Thrombin, Together with Observations on Antithrombin and Prothrombin, *Am. J. Physiol.* **26**:453, 1910.

33. Howell.<sup>10</sup> Gasser.<sup>11</sup> Footnote 12.

plasma and observing the variation in the clotting time.<sup>34</sup> These methods were developed before the standardization technic of thrombin by Smith and his co-workers by which they defined 1 unit as that amount which will convert 1 cc. of fibrinogen to fibrin in fifteen seconds. In my observations it was noted that a fraction of a unit of thrombin may remain active for a considerable time when added to serum. Whether small quantities are protected in some manner so as to prevent their inactivation is as yet unexplained. It is evident that the addition of small quantities of thrombin to serum does not give a true index of the antithrombic activity, because when larger amounts are added 74 to 147 units may be neutralized in four minutes. The antithrombic activity of diluted serum or plasma is not a true index of the ability of undiluted serum or plasma to neutralize thrombin, a correction factor being necessary for interpretation. The observed antithrombin in these studies is more than a thousandfold greater than the amount previously described in serum or plasma by the majority of investigators.

In theory, deviations from the physiologic range of antithrombin should affect blood coagulation, thrombosis tending to occur when it is depleted, hemorrhages when it is increased. In fact, certain pathologic states have been observed in which an abnormal antithrombin level has been thought to be a significant contributing factor in the syndrome. The hemorrhagic state in hypoprothrombinemia usually occurs at those levels at which the prothrombin unitage is within the same range as that of the antithrombin unitage as measured by the present method. Several factors must be considered to explain the hemorrhagic diathesis in the hypoprothrombinemic person, namely, the quantity and convertibility of prothrombin<sup>35</sup> and the quantitative level of antithrombin. This observed phenomenon further explains the hemorrhagic diathesis which occurs as a result of hypoprothrombinemia due to various causes. As has been previously stated, the decreased plasma prothrombin per se does not explain the hemorrhagic tendency because 1 unit of thrombin may clot 1 cc. of fibrinogen in fifteen seconds, normal human plasma containing three hundred times this amount in the form of its precursor prothrombin. A decrease in antithrombin in postoperative thrombosis has been reported by Howell<sup>10</sup> and Bancroft, Kugelmass and Stanley-Brown.<sup>36</sup> It is well established that antithrombin can be increased in vivo by act administration of heparin and Witte's peptone. Anaphylactic

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34. Quick.<sup>13</sup> Eagle, Johnston and Ravdin.<sup>14</sup>

35. (a) Warner, E. D.; Brinkhous, K. M., and Smith, H. P.: The Prothrombin Conversion Rate in Various Species, *Proc. Soc. Exper. Biol. & Med.* **40**:197-200, 1939. (b) Owen, C. A.; Hoffman, G. R.; Ziffrin, S. E., and Smith, H. P.: Blood Coagulation During Infancy, *ibid.* **41**:181-185, 1939.

36. Bancroft, F. W.; Kugelmass, I. N., and Stanley-Brown, M.: Evaluation of Blood Clotting Factors in Surgical Diseases, *Ann. Surg.* **90**:161-189, 1929.

shock results in either retarded or complete inhibition of blood clotting. Zunz and La Barre<sup>37</sup> explained this on the basis of an increase in antithrombin. Eagle, Johnston and Ravdin<sup>14</sup> have recently observed that anaphylactic shock in dogs and rabbits does not affect the prothrombin, fibrinogen, blood platelet or calcium level but does cause an extraordinary increase in antithrombin. This increase in antithrombin is due to an elevation in the heparin content of the blood. Jaques and Waters<sup>38</sup> have isolated crystalline heparin from the blood of dogs sensitized to horse serum and of dogs in anaphylactic shock produced during amytal anesthesia. Mills and Kitzmiller<sup>12</sup> have reported an increase in the antithrombin of the blood serum in patients with typhoid fever. Whether variations may be present in other pathologic states remains for future determination. Preliminary investigations seem to indicate that the antithrombin levels are not markedly altered in the majority of diseases.

#### SUMMARY

A quantitative test has been devised for the determination of the antithrombin of serum and plasma. One unit of antithrombin is defined as that amount which will inactivate 1 unit of thrombin in four minutes at 28 C.

Normal human plasma or serum contains an average of 90 units of antithrombin per cubic centimeter, which is as much as a thousand times the amount revealed by many of the previous methods.

There is little or no difference in the antithrombic activity of serum and that of plasma.

During the actual process of blood coagulation only a small portion of the thrombin is adsorbed onto fibrin, the remainder being inactivated or neutralized by the normal antithrombic activity of the serum.

The hemorrhagic tendency in hypoprothrombinemia is not, therefore, fully explained on the basis of decreased prothrombin and the variations in the conversion rate of prothrombin to thrombin. The hemorrhagic diathesis usually occurs when the prothrombin unitage approximates or is lower than the antithrombin unitage.

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37. Zunz, E., and La Barre, J.: Contribution à l'étude des modifications de la coagulation du sang au cours du choc anaphylactique chez le chien, *Arch. internat. de physiol.* **25**:221, 1925.

38. Jaques, L. B., and Waters, E. T.: The Isolation of Crystalline Heparin from the Blood of Dogs in Anaphylactic Shock, *Am. J. Physiol.* **129**:P389-P390, 1940.

# THERAPEUTIC AND PROPHYLACTIC DETOXICATION OF SULFANILAMIDE, SULFAPYRIDINE AND SULFATHIAZOLE

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The process of aiding the body with sulfanilamide compounds in its fight against a specific bacterial invasion presents simultaneously to the body toxic chemicals which it must detoxify. The processes used by the body in detoxication are oxidation, reduction and conjugation. Frequently, oxidation and reduction precede conjugation. The compounds involved in conjugative detoxication are well known; no attempt will be made to review the extensive material as various excellent reviews on the subject are available.<sup>1</sup> There is a certain specificity exhibited in the processes of detoxication. The compounds involved are aminoacetic acid, choline, cystine, glucuronic acid, glutamine, sulfates, acetates and ornithine.

The chemotherapeutic efficacy of the sulfanilamide compounds—sulfanilamide, sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine), sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole, etc.—against infections caused by such organisms as streptococci, pneumococci and staphylococci is well established. These compounds are toxic per se, manifesting in human beings a variety of symptoms.<sup>2</sup>

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From the Warner Institute for Therapeutic Research.

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A consideration of the literature on detoxication led us to attempt to decrease the toxicity of the sulfanilamide compounds without altering their chemotherapeutic efficacy. Generally, a reenforcement of the body's natural processes of detoxication was undertaken.

#### MATERIAL AND METHOD

*Subjects.*—A total of 7,000 white mice, 18 to 25 Gm. in weight, was used to study acute toxicities. Chemotherapeutic efficacy was tested on approximately 1,500 mice. Absorption speeds were determined in a series of 20 dogs. The degree of conjugation was determined in approximately 100 rats and 20 rabbits.

*Acute Toxicities.*—It was necessary to check the values given by various investigators for the oral lethal doses of the compounds used, sulfanilamide, sulfapyridine and sulfathiazole. It became evident from the outset that a multiplicity of factors affected the value, e. g., the suspending agent, the osmotic pressure of solutions in which the sulfanilamide compound was given, the diet of the mice before use, the hydrogen ion concentration of the aforementioned solutions, the weight of the mice and the usual biologic variation. Each of the controllable factors received appropriate attention in all experiments throughout the study.

All compounds used by the body in detoxication were regarded as potential detoxifying agents for sulfanilamide and its derivatives. Included among these compounds were cysteine, choline, aminoacetic acid, glutamine, sulfates, acetates and calcium glucuronate. A large number of other compounds of similar or unrelated structure were tried as potential detoxifying agents. All compounds tested are listed in table 1. Doses were usually administered at a level of 4 Gm. of sulfanilamide compound per kilogram of body weight. The detoxifying compound or mixture of compounds was fed at the same level, 4 Gm. per kilogram, except in specified instances. In the early experiments a 10 per cent solution of acacia was used as the suspending agent, but frequent unexplainable variation in control toxicity determinations led us to abandon acacia in favor of a 0.5 per cent solution of tragacanth. Volumes of material administered were held below 0.8 cc. It is possible to cause death in a series of animals by using 1.0 cc. doses of solutions which are osmotically active or which are not neutral in  $p_H$ . The sulfanilamide compound and the detoxifying chemical were administered in the same solution in the major portion of our experiments. A magnification of the detoxifying action is afforded if the detoxifying chemical is given several hours before the administration of the sulfanilamide compound. A long blunt syringe needle and a tuberculin syringe graduated in hundredths of a cubic centimeter were used throughout for oral administration. No group of animals less than 25 in number was considered, and no greater variation in weight than 4 to 6 Gm. in any set of 250 mice was permitted. The dietary regimen of the mice before use was controlled by maintaining them on a stock ration for several days and then placing them on an unpolished rice ration for three days before use. The latter diet is a maintenance ration, calorically adequate but inadequate nutritionally for other than maintenance. Diet before use is a most important factor. Diet variation can cause experimental results in control animals to vary by as much as 50 per cent. The solubilizing effect of possible variation in  $p_H$  was controlled by determinations of the absorption speeds of the compounds involved.

## RESULTS

*Sulfanilamide*.—Table 1 presents a summary of the results obtained with various compounds and combinations of compounds in detoxifying sulfanilamide.

It is evident from these results that the toxicity of sulfanilamide can be significantly reduced by the simultaneous administration of even single doses of compounds used by the body in the general processes of detoxication.

TABLE 1.—*Protection Afforded by Various Physiologic Detoxifying Agents and Combinations of These Agents Against Acutely Toxic Doses of Sulfanilamide, Expressed in Terms of the Decrease in the Percentage Mortality Rate\**

Questionable Decrease or None	20% Decrease	40% Decrease
Glutamic acid	Sodium acetate	{Cysteine hydrochloride
Nicotinic acid	Calcium gluconate	{Glutamic acid
Thiamine hydrochloride	Choline	{Aminoacetic acid
Sodium sulfate		{Ascorbic acid
Alanine	{Calcium glucuronate	{Calcium glucuronate
Serine	{Ferrous chloride	
Leucine		Calcium glucuronate
Isoleucine	Liquid yeast concentrate	
Valine	Methionine	{Cystine
Mucic acid	Calcium aldobionate	{Aminoacetic acid
Levulose	Arabinic acid	{Calcium glucuronate
Aldohexoses	2-ketogluconic acid	{Ascorbic acid
Dihydroxyacetone	Saccharolactone	
Lactic acid	Glutamine	Ascorbic acid
Pyruvic acid	Cysteine hydrochloride	
Saccharic acid	Aminoacetic acid	
Pectic acid	Isoascorbic acid	
Glyoxallic acid		
Sodium propionate		
Lecithin		
Cephalin		
Cholesterol		
Xanthine		
Adenine		
Guanine		
Acetaldehyde		
Ornithine		

\* Compounds bracketed together were administered in combination.

In summary, the acute toxic effects of sulfanilamide in albino mice can be reduced by as much as 40 per cent by the simultaneous administration of single doses of compounds used by the body in detoxication. Calcium glucuronate was found to be the most efficacious single one of these compounds. A combination of aminoacetic acid, cystine, calcium glucuronate and ascorbic acid was observed to provide the most consistent and the greatest protection.

With this pronounced reduction in toxicity, the question immediately arises as to whether the chemotherapeutic efficacy has been reduced. To test this, the same solutions were used to protect white mice, 18 to 22 Gm. in weight, against a streptococcic infection. The therapeutic dose of sulfanilamide used was 2 Gm. per kilogram, given with and without the simultaneous administration of a detoxifying chemical or chemicals.

The detoxifying chemicals were also tested in the absence of the sulfanilamide for possible direct action. The products of bacterial metabolism are known to be extremely toxic; thus an obvious potentiality presented itself. The inoculum used was 0.1 cc. of an undiluted broth culture of *Streptococcus haemolyticus*. An attempt was made to hold this dose of the bacteria at such a level as to kill less than 100 per cent of the animals in the negative control series. The dose of sulfanilamide was then adjusted to afford a difference in death rate percentages of 20 to 40 or 50. The results of testing the chemotherapeutic efficacy of sulfanilamide in the presence of various detoxifying chemicals show conclusively that there is no decrease in the chemotherapeutic efficacy of sulfanilamide. On the contrary, there seems to be a slight but definite enhancement of the antistreptococcus activity. There was a difference in the percentage death rates of approximately 10 in the 3,000 mice used. Furthermore, an extension of the survival period is seen when the

TABLE 2.—*Absorption Speed of Sulfanilamide as Influenced by Detoxifying Chemicals\**

Hour	Dose: 1.0 Gm. of Sulfanilamide With 1.0 Gm. of Detoxifying Mixture	Dose: 1.0 Gm. of Sulfanilamide Without Any Detoxifying Mixture
1.....	3.79	3.96
2.....	6.74	5.46
3.....	10.03	7.65
4.....	8.13	6.86

\* Values are expressed in milligrams of sulfanilamide per hundred cubic centimeters of blood and represent the average for 4 dogs.

detoxicant is given to mice with streptococcic infections. The detoxicant alone both extends the survival period of these mice and causes a slight decrease in the percentage of deaths due to the infections.

To check further the possibility that decreased absorption may have been a factor in the decreased toxicities observed, dogs were given doses of 1 Gm. of sulfanilamide, first without an added detoxifying agent, then with the detoxifying compound or mixture of compounds and finally again without the detoxifying chemical. The concentration of sulfanilamide in the blood was measured hourly by the method of Bratton and Marshall.<sup>3</sup> In each instance the three determinations were carried out on the same dog, in order to eliminate any factors varying from animal to animal. The results observed in the case of sulfanilamide are recorded in table 2.

Clearly, there is no decrease in the speed of absorption and the maximum concentration reached is not diminished when the detoxicant is given with the sulfanilamide. It is obvious, therefore, that the decreased

3. Bratton, A. C., and Marshall, E. K., Jr.: New Coupling Component for Sulfanilamide Determination, *J. Biol. Chem.* **128**:537, 1939.



toxicity of sulfanilamide given with one or more detoxifying chemicals cannot be traced to decreased absorption. The results would even indicate an increased absorption to the extent of approximately 10 per cent, which possibly may be a factor in the increased chemotherapeutic efficacy of sulfanilamide when administered with the detoxifying compounds.

In summary, we have demonstrated that the administration of sulfanilamide with a detoxifying chemical decreases the toxicity of sulfanilamide by as much as 40 per cent, increases its chemotherapeutic efficacy against *Str. haemolyticus* by 10 per cent and increases the speed of its absorption from the gastrointestinal tract by approximately 10 per cent.

*Sulfapyridine*.—Using 700 mice and the technic employed in the study of sulfanilamide, we found that the acute toxicity of sodium sulfapyridine was reduced by as much as 50 per cent by the simultaneous admission of detoxifying chemicals. Aminoacetic acid and ascorbic acid seemed to be the most effective single detoxifying chemicals. Again, to determine the effect on chemotherapeutic efficacy, we administered sodium sulfapyridine with and without a detoxifying mixture to animals with infections caused by pneumococci of type II. From the results of a study involving 750 mice, it can be concluded that there was a distinct shift in the percentage of deaths for each day. The presence of the detoxifying chemicals brought about a distinct prolongation of the survival period of the entire series. As in the case of sulfanilamide, the absorption speed of the sodium sulfapyridine with and without the detoxicant was measured in 6 dogs. The results showed that there is no decrease in the speed of absorption and the maximum concentration reached is not diminished when the detoxicant is given with the chemotherapeutic agent.

*Sulfathiazole*.—Five hundred mice were used in testing the activity of detoxifying chemicals in acute sodium sulfathiazole intoxication. Here, as in the case of sodium sulfapyridine, the number of deaths in the entire series was reduced by as much as 50 per cent. Cystine and aminoacetic acid seemed to be the two chemicals which individually exerted the greatest effect in combating sodium sulfathiazole intoxication. The chemotherapeutic efficacy against pneumococci of type II of sodium sulfathiazole given with and without the detoxifying chemicals was tested in a series of 750 mice. That the animals receiving detoxifying chemicals were protected was manifested in prolonged survival periods. The absorption speed was not altered by the concomitant administration of detoxifying chemicals.

#### COMMENT

The sulfanilamide compounds (sulfanilamide, sulfapyridine and sulfathiazole) must be detoxified by oxidation or reduction and subsequent conjugation. Acetylation of sulfanilamide has been demonstrated in the

human subject and in the rabbit by Marshall and associates,<sup>4</sup> and Harris and Klein<sup>5</sup> first demonstrated that it takes place in the liver. Acetylation both of sulfanilamide and of sulfapyridine was described for the cat by van Winkle and Cutting.<sup>6</sup> The liver was again designated as the site of detoxication. Conjugation seems to be the final and essential step in detoxication. Recoveries of between 50 and 95 per cent of ingested sulfanilamide have been reported,<sup>7</sup> and a portion of this amount is conjugated as the acetyl derivative. The question remains as to whether all ingested sulfanilamide can be accounted for by the excretion of free and acetylated forms or whether it is excreted partly in some other form, such as the glucuronide. This potentiality has been strengthened by the observation of Scudi and associates<sup>8</sup> that increased glucuronate excretion followed the administration of sulfapyridine, and more recently, Scudi<sup>9</sup> has demonstrated hydroxysulfapyridine in dog urine and has isolated a water-soluble glucuronate of hydroxysulfapyridine. James<sup>10</sup> raised the question of the exact manner in which sulfanilamide and acetylsulfanilamide exerted their toxic action. He suggested that while the acetyl derivative had a direct toxic action, sulfanilamide killed by a sudden withdrawal of acetate precursors in the body. The toxicity of sulfapyridine was also attributed to the withdrawal of acetate ions. He observed a significant decrease in the toxicity both of sulfanilamide and of sulfapyridine when sodium acetate was given at the same time. Our results with sulfanilamide, sulfapyridine and sulfathiazole confirm the observations of James, but the decrease in toxicity is less marked with sodium acetate than with certain other detoxifying chemicals. There is some evidence in the literature contraindicating the use of acetates with the sulfanilamide compounds. Lehr and co-workers<sup>11</sup> have demonstrated that

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4. Marshall, E. K., Jr.; Cutting, W. C., and Emerson, K., Jr.: Acetylation of *p*-Aminobenzene Sulfonamide in Animal Organism, *Science* **85**:202, 1937.

5. Harris, J. S., and Klein, J. R.: Acetylation of Sulfanilamide by Liver Tissue in Vitro, *Proc. Soc. Exper. Biol. & Med.* **38**:78, 1938.

6. van Winkle, W., Jr., and Cutting, W. C.: Acetylation of Sulfanilamide and Sulfapyridine in the Cat, *J. Pharmacol. & Exper. Therap.* **69**:40, 1940.

7. Stewart, J. D.; Rourke, G. M., and Allen, J. S.: Excretion of Sulfanilamide, *J. A. M. A.* **110**:1885 (June 4) 1938. Scudi, J. V., and Ratish, H. D.: Urinary Excretion of Single Dose of Sulfanilamide, *J. Lab. & Clin. Med.* **23**: 615, 1938. Marshall, E. K., Jr.; Emerson, K., Jr., and Cutting, W. C.: Para-aminobenzene Sulfonamide: Absorption and Excretion; Method of Determination in Urine and Blood, *J. A. M. A.* **108**:953 (March 20) 1937.

8. Scudi, J. V.; Ratish, H. D., and Bullowa, J. G. M.: Increased Glucuronate Excretion Following Administration of Sulfapyridine, *Science* **89**:516, 1939.

9. Scudi, J. V.: On Urinary Excretion of Sulfapyridine, *Science* **91**:486, 1940.

10. James, G. V.: Effect of Administration of Acetate on Detoxication and Therapeutic Activity of Sulphanilamide, *Biochem. J.* **33**:1688, 1939; **34**:633, 1940.

11. Lehr, D.; Antopol, W., and Churg, J.: Massive "Acute" Precipitation of Free Sulfathiazole in the Urinary Tract, *Science* **92**:434, 1940.

acetylated sulfathiazole precipitated in massive amounts in the urinary tract, causing sudden death in mice. The bladders of these animals on occasion became completely filled with the white crystalline material. Increased acetylation might aggravate the tendency of sulfathiazole to precipitate in the bladder as the acetylated derivative. Furthermore, Marshall and associates<sup>12</sup> stated that acetylsulfanilamide is more toxic when administered parenterally than is sulfanilamide itself. We have attempted to decrease the amount of acetylation by forcing conjugation into other channels, such as the formation of glucuronate. The administration of a detoxifying mixture containing cystine, aminoacetic acid, calcium glucuronate and ascorbic acid has been demonstrated<sup>13</sup> to decrease the acetylation of sulfanilamide in the rat.

Klein and Harris<sup>14</sup> studied the acetylation of sulfanilamide in vitro. They showed that acetylation of this compound can occur in slices of liver and that the factor limiting the reaction in speed is the rate of acetate production by the tissue. Addition of acetate increases the amount of conjugation, as does the addition of substances giving rise to acetate in the tissue. Pyruvate, lactate and acetoacetate had a variable effect in increasing conjugation, but acetate was constant in its effect.

Southworth<sup>15</sup> was the first to observe the fall of the carbon dioxide-combining power of the blood of patients treated with sulfanilamide. Hartmann, Perley and Barnett<sup>16</sup> then suggested the use of sodium lactate and Lucas and Mitchell<sup>17</sup> suggested sodium bicarbonate to counteract this fall. Lactate and bicarbonate would both raise the carbon dioxide-combining power, but the lactate has the advantage of being an acetyl precursor. The use of acetate, according to the work of James,<sup>18</sup> during the administration of a sulfanilamide compound offers certain advantages in modifying its acute toxicity, and James's experiments show that it acts by preventing the metabolism of acetate precursors. Other substances, such as lactate and bicarbonate, have been suggested for counteracting a fall in carbon dioxide-combining power, but acetate has this effect and in addition provides acetyl radical directly. James<sup>18</sup> also

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12. Marshall, E. K., Jr.; Cutting, W. C., and Emerson, K., Jr.: The Toxicity of Sulfanilamide, *J. A. M. A.* **110**:252 (Jan. 22) 1938.

13. Martin, G. J.; Rennebaum, E. H., and Thompson, M. R.: Inhibition of Conjugation of Sulfanilamide, *J. Biol. Chem.* **139**:871, 1941.

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15. Southworth, H.: Acidosis Associated with Administration of Paraamino-benzene Sulfonamide (Prontylin), *Proc. Soc. Exper. Biol. & Med.* **36**:58, 1937.

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17. Lucas, C. C., and Mitchell, D. R.: Biochemical Study of Patients on Sulphanilamide Therapy, *Canad. M. A. J.* **40**:27, 1939.

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clearly demonstrated that oxidation is a primary detoxicating mechanism for the sulfanilamide compounds. Para-N-acetylhydroxylaminobenzene-sulfonamide, parahydroxyaminobenzenesulfonic acid and paraaminophenol were isolated from the urine of patients treated with sulfanilamide. James stated that these compounds appear to be excreted in conjugation with sulfates and glucuronates. The paraaminophenol undergoes further changes and is excreted as a pigment.

It is desired to point out that the action of the detoxifying chemical or chemicals is not specific for the sulfanilamide compounds under consideration in this paper but rather is a manifestation of a reenforcement of the processes ordinarily used by the body in its defense against toxic chemicals, regardless of their nature. This type of therapeutic or prophylactic detoxication is equally effective against the products of the metabolism of the organisms which invade the body and the specific chemotherapeutic agents used in the treatment of diseases caused by these organisms. The problem of the detoxication of absorbed toxic chemicals is the same as the problem of the detoxication of toxic chemicals produced within the body by an invading parasite. The general process of detoxication follows three lines: oxidation, reduction and conjugation. Frequently, oxidation and reduction precede conjugation. The processes of oxidation and reduction of toxic chemicals are being subjected to intensive study, but it remains difficult to apply any practical means of influencing these processes. Vitamin therapy doubtless owes a great deal of its effectiveness to the reestablishment of an enzyme moiety and normal processes of oxidation and reduction which are concerned in detoxication. Thus, there is available at present but one process which can be used to facilitate detoxication, namely, the process of conjugation. In passive immunity the body's defense is reenforced by supplying additional preformed antibodies. In conjugative detoxication it is possible to supply the body with an increased amount of the raw materials used in the processes of detoxication.

#### SUMMARY

The acute toxicities of sulfanilamide, sulfathiazole and sulfapyridine were markedly reduced by the prophylactic and therapeutic use of physiologic detoxifying chemicals, such as cystine, aminoacetic acid, calcium glucuronate and ascorbic acid.

The chemotherapeutic efficacy of the sulfanilamide compounds when administered with detoxifying chemicals was maintained or enhanced.

The speed of absorption was increased when a sulfanilamide compound was administered with detoxifying chemicals.

Therapeutic and prophylactic detoxication offers tremendous potentialities for clinical application.

# RENAL LESIONS FOLLOWING THE INTRAVENOUS INJECTION OF A HYPERTONIC SOLUTION OF SUCROSE

A CLINICAL AND EXPERIMENTAL STUDY

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Sucrose has been widely used for tissue dehydration in such conditions as cerebral edema associated with trauma,<sup>1</sup> chronic hypertension,<sup>2</sup> acute alcoholism,<sup>3</sup> status asthmaticus,<sup>4</sup> postoperative anemia,<sup>5</sup> edema of nephrosis and nutritional edema.<sup>6</sup>

The quantity and the concentration of sucrose given to patients have varied widely. Dyar and Matthew<sup>7</sup> gave 400 cc. of a 25 per cent solution intravenously. These investigators found no contraindication to the use

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2. Murphy, F. D.; Hershberg, R. A., and Katz, A. M.: The Effect of Intravenous Injections of Sucrose Solution (50 Per Cent) on the Cerebrospinal Fluid Pressure, the Blood Pressure and Clinical Course in Cases of Chronic Hypertension, *Am. J. M. Sc.* **192**:510, 1936.

3. Hilton, J. P., and Alderson, D. M.: Sucrose Solution in the Treatment of Alcoholism and Confusional States, *Rocky Mountain M. J.* **35**:227, 1938.

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6. Lowenburg, H., and Nemser, S.: Intravenous Injection of Fifty Per Cent Solution of Sucrose in Edema, *Arch. Pediat.* **53**:762, 1936. Lowenburg, H., and Miller, A. B.: A Case of Nutritional Edema, *ibid.* **55**:297, 1938.

7. Dyar, E. W., and Matthew, W. B.: Use of Sucrose Preparatory to Surgical Treatment of Glaucoma, *Arch. Ophth.* **18**:57 (July) 1937.

of sucrose except perhaps the presence of markedly low renal function. Masserman<sup>8</sup> has given intravenously as much as 500 cc. of a 50 per cent solution of sucrose. He expressed the opinion that "comparatively large amounts of sucrose in the circulation are not toxic and cause no serious disturbances in the chemistry or cytology of the blood." Keith and Power<sup>9</sup> found "the total excretion of the various urinary constituents during a day in which sucrose is injected but slightly altered aside from changes that may be attributed to diuresis." Murphy and his associates<sup>2</sup> gave 300 to 500 cc. of a 50 per cent solution of sucrose to 21 patients with chronic hypertension. The patients improved, and no unfavorable results were noted from the treatment.

Cutler<sup>10</sup> apparently was the first to give any information as to the quantity of sucrose that may safely be administered to patients. He concluded from his histologic studies of human kidneys that sucrose may produce renal lesions when approximately 6 to 10 Gm. per kilogram of body weight is given in a week.

The renal lesions that may occur in man after the injection of sucrose have been described by Helmholz,<sup>11</sup> Cutler,<sup>10</sup> Anderson and Bethea<sup>12</sup> and Anderson.<sup>13</sup> The pathologic process has been nicely described and well illustrated by the two last-named authors. The epithelial cells in the convoluted portion of the renal tubules become markedly swollen, and the cytoplasm is foamy. This change has been observed both as a focal and as a diffuse lesion.

In reviewing the clinical cases reported by Anderson and Bethea<sup>12</sup> and Anderson<sup>13</sup> we have been impressed with the fact that other investigators have given more sucrose to their patients without the development of any renal lesions. Anderson<sup>13</sup> discussed the probability that "pre-existing renal lesions may enhance the effects of sucrose on

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9. Keith, N. M., and Power, M. H.: The Urinary Excretion of Sucrose and Its Distribution in the Blood After Intravenous Injection into Normal Men, *Am. J. Physiol.* **120**:203, 1937.

10. Cutler, H. H.: Effect of Sucrose on the Kidney, *Proc. Staff Meet., Mayo Clin.* **14**:318, 1939.

11. Helmholz, H. F.: Renal Changes in the Rabbit Resulting from Intravenous Injection of Hypertonic Solution of Sucrose, *J. Pediat.* **3**:144, 1933.

12. Anderson, W. A. D., and Bethea, W. R., Jr.: Renal Lesions Following Administration of Hypertonic Solutions of Sucrose, *J. A. M. A.* **114**:1983 (May 18) 1940.

13. Anderson, W. A. D.: Sucrose Nephrosis and Other Types of Renal Tubular Injuries, *South. M. J.* **34**:257, 1941.

the tubules so that changes are produced from relatively small amounts." He asserted:

Sucrose nephrosis was found to be severe in kidneys involved by marked vascular disease. It may well be that interference with renal circulation by vascular change, or a similar effect produced by thickening of glomerular basement membrane, will markedly enhance the damaging effect of sucrose. Particularly if there was a reduction in filtration rate, it would operate to prolong the exposure of the epithelial cells to the sucrose in the filtrate.

In considering Anderson's explanation of the effect of previous renal disease on the development of tubular lesions following the injection of sucrose, it must be remembered that Murphy, Hershberg and Katz<sup>2</sup> gave 300 to 500 cc. of a 50 per cent solution of sucrose to 21 patients with chronic hypertension. This treatment relieved such symptoms as headache, vomiting, vertigo, twitching and dizziness. No unfavorable results were observed in any of the 21 patients.

Lindberg and associates<sup>14</sup> gave 200 cc. of a 50 per cent solution of sucrose to 15 persons without any renal damage.

In no case was there evidence of marked impairment of renal function. An occasional specimen of urine after the injection showed a 1 plus reaction for albumin or hyaline casts. The urea clearance remained essentially stationary, and in some cases it was increased by 3 to 5 per cent . . . Five patients with known renal damage were similarly studied. In these, too, the urine and urea clearance showed no significant changes as a result of the injection of 200 cc. of sucrose intravenously.

The following factors have impressed us in reviewing the autopsy reports on a group of patients who were given sucrose: (1) the quantity of sucrose administered; (2) the state of dehydration at the time the sucrose was injected, and (3) the fluid intake and output during the period in which sucrose was given. The following case reports will illustrate these factors.<sup>15</sup>

#### REPORT OF SIXTEEN CASES

CASE 1.—A white man aged 64 became comatose two days before admission. He lived four hours after hospitalization and only three hours after the intravenous injection of 200 cc. of a 25 per cent solution of sucrose.

Generalized arteriosclerosis, with an occlusion in the left coronary artery and a recent myocardial infarct, was evident at autopsy. Scars were also present

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14. Lindberg, H. A.; Wald, M. H., and Barker, M. H.: Renal Changes Following Administration of Hypertonic Solutions, *Arch. Int. Med.* **63**:907 (May) 1939.

15. Cases 1, 2, 3, 4, 6, 7 and 10 have been included in previous papers by Anderson and Bethea<sup>12</sup> and Anderson.<sup>13</sup> Dr. W. D. Forbus, professor of pathology, Duke University, has permitted us to include cases 13 to 16. Dr. A. J. Gill, of Duke University, summarized the histories of these cases.

in the myocardium. The cavities of the heart were dilated, and the viscera were congested. Bronchopneumonia was present. The renal arteries were sclerotic. The epithelial cells in the convoluted portion of the tubules were swollen, and their cytoplasm was foamy.

The three hour interval between the injection of sucrose and death was the shortest period which has elapsed between injection of sucrose and postmortem study of the kidneys in this series. It illustrates the rapidity with which the renal lesion may develop. The histologic changes in this case were similar to those observed in cases in which death occurred several days after the injection of sucrose. The fluid intake no doubt was small before hospitalization, since the patient was unconscious. The amount of fluid lost through the skin should have been large, since he died in June. This case illustrates the role that dehydration may play in the subsequent development of tubular changes following the injection of sucrose.

There was no evidence from the histologic studies that a pathologic condition existed in the kidneys before the patient received the sucrose.

CASE 2.—A Negro aged 67 gave a history of a severe headache of three months' duration. He became drowsy, and the muscles of the upper extremities began to twitch. He became unconscious three hours before admission and remained comatose until death. He died thirty-six hours after hospitalization.

The temperature on admission was 104 F., the pulse rate 130 per minute, the respiratory rate 32 to 40 per minute and the blood pressure 140 systolic and 85 diastolic. The spinal fluid pressure equaled 218 mm. of water. The specific gravity of the urine was 1.023, and the albumin present gave a 2 plus reaction. Occasional white blood cells and casts were found in each high power field. The blood contained 30 mg. of nonprotein nitrogen per hundred cubic centimeters. The numbers of white cells and red cells and the quantity of hemoglobin in the blood were normal.

During the thirty-six hours of hospitalization the patient was given a total of 1,000 cc. of a 25 per cent solution of sucrose intravenously and 14 cc. of a 50 per cent solution of magnesium sulfate intramuscularly.

Generalized arteriosclerosis was observed at autopsy. Small hemorrhages were present in the endocardium. The prostate gland was hypertrophied. Bronchopneumonia was present. The cortex of the kidneys was slightly scarred. Apparently every epithelial cell in the convoluted portion of the renal tubules was markedly swollen, and the cytoplasm was foamy. An albuminous precipitate was present in Bowman's space in some of the glomeruli and in the lumen of some of the tubules.

This patient apparently had some renal insufficiency before receiving the sucrose. There are not enough data to determine the state of hydration.

CASE 3.—A white man aged 74 gave a typical history and showed the classic signs of myocardial failure on admission. A systolic murmur could be heard over the entire precordium. The temperature was 96.4 F., the respiratory rate 30 per minute, the pulse rate 88 per minute and the blood pressure, 130 systolic and 70 diastolic. The patient lived only a day and a half in the hospital. On admission the blood contained 30 mg. of nonprotein nitrogen per hundred cubic centimeters. Eleven and a half hours before death he was given 200 cc. of a 25 per cent solution of sucrose intravenously.

Healed rheumatic endocarditis of the aortic and the mitral valve, with stenosis, was evident at autopsy. The heart was hypertrophied, and the cavities



were dilated. Chronic passive congestion and generalized arteriosclerosis were present. Precipitated protein was present in Bowman's space in some of the glomeruli. Apparently, every epithelial cell in the convoluted portion of the renal tubules was swollen, and the cytoplasm was foamy.

The presence of a normal amount of nonprotein nitrogen in the blood on admission would suggest a relatively normally functioning kidney. Protein in Bowman's spaces, observed histologically, may have resulted from the chronic passive congestion. This case illustrates the diffuse tubular injury that may follow the intravenous injection of sucrose. It is the only case in this series in which the patient had severe edema at the time the sucrose was given.

CASE 4.—A white woman aged 69 became unconscious at 7:30 a. m., while eating breakfast, and thereafter was unable to speak. She vomited dark, blood-like material on several occasions. Thirty minutes after this accident the patient was admitted to the hospital. She was unconscious but apparently not completely paralyzed. The temperature was 97 F., the pulse rate 96 per minute, the respiratory rate 36 per minute and the blood pressure 145 systolic and 68 diastolic. The spinal fluid was bloody. She was given 2 cc. of a 50 per cent solution of magnesium sulfate intramuscularly and 100 cc. of a 25 per cent solution of sucrose intravenously. Death occurred fourteen hours after the cerebral accident and twelve hours after the intravenous injection of sucrose.

A ruptured aneurysm at the bifurcation of the right internal carotid artery was evident at autopsy. Blood had dissected into the ventricles of the brain. The cavities of the heart were dilated, and the viscera showed the changes associated with venous congestion. The epithelial cells in the convoluted portion of the renal tubules were swollen and granular. The cytoplasm of these cells was not as "foamy" as has been observed in other patients given sucrose. There were a few scars in the cortex and focal collections of lymphocytes in the interstitial tissues.

The quantity of sucrose given to this patient was only half that given to others in whom tubular lesions occurred. Nothing in the kidneys indicated previous renal disease. The tubular changes which may have resulted from the administration of sucrose were indefinite. This case is important only because of the small quantity of sucrose which was administered and the absence of definite tubular lesions attributable to the sucrose.

CASE 5.—A white man aged 68 fell unconscious approximately three hours before admission to the hospital. After a few minutes consciousness returned; however, within thirty minutes he again lapsed into coma. He was paralyzed on the right side of the body. Coma persisted, and death occurred forty-eight hours after admission to the hospital.

The patient was given 84 ounces (2,484 cc.) of milk and fruit juices through a Levin tube during hospitalization. Twelve hours before death he was given 100 cc. of a 25 per cent solution of sucrose intravenously.

A generalized arteriosclerotic process, with a cerebral hemorrhage in the area of the right internal capsule, was apparent at autopsy. The heart was hypertrophied, and the cavities were dilated. The viscera were congested. Arteriosclerosis was present both in the large and in the small arteries of the kidneys. The arterioles also were thickened. Scars and collections of lymphocytes were present in the interstitial tissue of the renal cortex. The epithelial cells lining the convoluted portion of the tubules were swollen, and the cytoplasm was finely

granular. The changes resembled those observed in cloudy swelling more than they did the tubular lesions that occur after the injection of sucrose.

The tubular lesions in this case may have been the result of the administration of sucrose; however, at this time there is nothing by which we can differentiate them from cloudy swelling. There are insufficient data to determine the degree of renal function and the state of hydration at the time the sucrose was given.

CASE 6.—A Negro aged 33 gave a history of severe, generalized headache and dizziness of three months' duration, spots before the eyes and progressive failure of vision. Massive hemorrhages, papilledema and exudates were present in the retina.

The blood pressure was 220 systolic and 163 diastolic, the temperature 99 F., the pulse rate 100 per minute and the respiratory rate 32 per minute. The urine had a specific gravity of 1.016 and gave a 2 plus reaction for albumin. Microscopic examination of an uncentrifuged specimen showed 5 to 8 white cells, an occasional red cell and 1 granular cell per high power field. The spinal fluid pressure equaled 300 mm. of water. There was moderate anemia. The hemoglobin content was 11.5 Gm. per hundred cubic centimeters of blood. On the third day in the hospital the patient became nauseated and vomited; he appeared lethargic and progressively became comatose. He died eight hours after the last injection of sucrose. The following data appear to be important:

Date	Course of Illness	Magnesium Sulfate, Orally, Oz.	25% Solution of Sucrose, Intravenously, Cc.	5% Solution of Dextrose, Intravenously, Cc.	Nonprotein Nitrogen in Blood, Mg. per 100 Cc.	Output of Urine, Cc.
5/2/39	Admission	...	...	.....	...	.....
5/3/39	.....	1.5	...	.....	75	1,000
5/4/39	.....	...	...	2,000	85	950
5/5/39	.....	1.5	750	.....	...	3,800
5/6/39	.....	...	...	.....	...	600 -
5/7/39	.....	1.5	...	500	...	1,300
5/8/39	Death	...	500	1,500	130	700

Severe, malignant arteriosclerosis was evident at autopsy. The heart was hypertrophied, and the cavities were dilated. Chronic passive congestion of the viscera and bronchopneumonia were present. The epithelial cells of many of the renal tubules were swollen, and the cytoplasm was foamy. The cells lining other convoluted tubules were small and stained deeply with hematoxylin. These did not show the swelling that may accompany the injection of sucrose.

The clinical and pathologic findings indicated severe nephritis, with renal insufficiency. This was present when the patient was admitted. The quantity of sucrose and magnesium sulfate given to this man apparently was sufficient to produce some dehydration. The most interesting pathologic process observed in this case resulted from the distribution of the renal lesions. The low cuboidal cells lining the convoluted portion of some renal tubules were not affected, while corresponding cells in other tubules were swollen and the cytoplasm was foamy.

CASE 7.—A Negress aged 60 complained of a sharp pain in the right temporal region on the day preceding admission to the hospital. At 2 a. m. on the day of admission she was found unconscious in bed. She was admitted to the hospital sixteen hours afterward. Coma was present and persisted until death, which

occurred twelve hours later. All the muscles were spastic. The reflexes were hyperactive in the upper extremities. The temperature was 101 F., the pulse rate 120 per minute, the respiratory rate 38 per minute and the blood pressure 200 systolic and 120 diastolic. The urine gave a 4 plus reaction for albumin. On admission the patient was sweating profusely. Her husband stated that she also sweated much during the night.

The patient was given 4 cc. of a 50 per cent solution of magnesium sulfate intramuscularly and 250 cc. of a 25 per cent solution of sucrose intravenously immediately after admission to the hospital. She died eleven hours after the injection of the sucrose.

Necropsy showed generalized arteriosclerosis and a cerebral hemorrhage into the right internal capsule. The blood had dissected into the ventricles. The heart was hypertrophied. There was an extensive arteriolosclerotic process in the kidneys. Some of the glomeruli were fibrosed. Areas of fibrosis and foci of lymphocytes were present in the cortex. In some focal areas the convoluted portion of the tubules were swollen and the cytoplasm was foamy. In other areas the epithelial cells were small and pyknotic.

There was both clinical and pathologic evidence of renal insufficiency. It was present preceding the injection of the sucrose. The absence of tubular lesions in those portions of the convoluted tubules in which the cells appeared to be of the regenerative type was interesting in view of the fact that a similar process was observed in cases 6 and 8. This patient, no doubt, was dehydrated on admission, since she had been unconscious for about sixteen hours. There was also a history of profuse sweating.

CASE 8.—A Negro aged 65 was paralyzed on the left side of the body on admission. No history was obtained. The spinal fluid was xanthochromic. The temperature was 99 F., the pulse rate 66 per minute, the respiratory rate 18 per minute and the blood pressure 134 systolic and 100 diastolic. The Kahn reaction of the blood was negative. A specimen of urine obtained by catheterization had a specific gravity of 1.024 and showed neither albumin nor sugar. The blood contained 30 mg. of nonprotein nitrogen per hundred cubic centimeters. There was severe anemia.

On the seventh day before his death the patient was given 100 cc. of a 50 per cent solution of sucrose intravenously and on the following day an additional 50 cc. Clinical signs of bronchopneumonia developed on the third day before death. The urinary output for six of the seven days preceding death was as follows: seventh day, 550 cc.; sixth day, 300 cc.; fifth day, 850 cc.; fourth day, 550 cc.; third day, 440 cc., and second day, 1,300 cc.

Generalized arteriosclerosis was evident at autopsy. A hemorrhage in the area of the internal capsule on the right side had ruptured into the lateral ventricle. Bronchopneumonia was present. Some of the glomeruli were fibrosed. The walls of a few of the arterioles were thickened. Hyaline casts were present in the lumens of some of the tubules. The epithelial cells in the convoluted tubules in focal areas of the kidneys were swollen, and the cytoplasm was foamy.

There was little if any evidence from either the clinical or the autopsy observations to indicate that renal disease existed at the time the patient was admitted to the hospital. The urinary output was low. This apparently was the result of a low intake of fluid. The tubular lesions were characteristic of those that may follow the injection of sucrose. The focal distribution of these lesions was interesting, since they occur often uniformly throughout the kidneys.

CASE 9.—On admission to the hospital a Negro aged 65 gave a history of severe headaches, occasional attacks of dizziness and pain in the back of three weeks' duration. The muscles of the upper extremities and the shoulders contracted involuntarily. The blood pressure was 270 systolic and 140 diastolic. A specimen of urine obtained by catheterization had a specific gravity of 1.012 and gave a 3 plus reaction for albumin. Microscopic examination of an uncentrifuged specimen showed 3 to 5 white cells per high power field. The white cell count was 21,100 and the red cell count 3,890,000 per cubic millimeter. There was 9.5 Gm. of hemoglobin per hundred cubic centimeters of blood. The Kahn reaction was negative.

The patient became stuporous and then comatose. He died six days after admission.

The following pertinent data were recorded day by day:

Date	Course of Illness	50% Solution of Magnesium Sulfate, Intramuscularly, Cc.	25% Solution of Sucrose, Intravenously, Cc.	Solution of Dextrose		Route *	Non-protein Nitrogen in Blood, Mg. per 100 Cc.	Output of Urine, Cc.
				Amount, Cc.	Concentration			
4/22/39	Admission	16	200	2,000	5%	I.V. S.C.	166	3,800
4/23/39	.....	16	500	4,000	5%	I.V. S.C.	...	3,400
4/24/39	.....	8	950	4,000	5%	I.V. S.C.	...	5,150
4/25/39	.....	12	750	3,000	5% 10%	S.C. I.V.	...	2,600
4/26/39	.....	8	400	3,000	5% 10%	S.C. I.V.	107	2,600
4/27/39	.....	4	600	2,000	5% 10%	I.V. S.C.	...	400
4/28/39	Death	8	225	2,000	5% 10%	I.V. S.C.	...	...

\* I.V. indicates intravenous; S.C., subcutaneous.

Autopsy revealed hypertrophy of the prostate gland, acute urethritis, acute cystitis and acute and chronic pyelonephritis. Pulmonary emboli and bronchopneumonia were present in both lungs. Arteriosclerotic nephritis was present, with red blood cells and albumin in the lumens of the renal tubules. Essentially every epithelial cell in the convoluted portion of the tubules was swollen, and the cytoplasm was foamy.

There was definite renal insufficiency at the time the patient was admitted to the hospital. The daily intake and output of fluid apparently were sufficient. The quantity of sucrose (3,625 cc.) that the patient received during a period of seven days apparently was too much regardless either of the fluid balance or of the state of renal function.

CASE 10.—A Negress aged 15 was approximately nine months pregnant. There was some edema of the feet and ankles. She gave a history of headaches for four or five months. A week before admission she had "blind staggers." Her family stated that the patient had had at least twenty-five convulsions on the day of admission. She was comatose, and edema of the lungs was present at the time of hospitalization.

The urine had a specific gravity of 1.009, gave a 3 plus reaction for albumin and a positive reaction for acetone and contained white and red blood cells. On

two occasions the blood level of nonprotein nitrogen was 26 and 30 mg. per hundred cubic centimeters. The white cell count was 21,000; the red cell count was 3,200,000, and the hemoglobin content was 9.4 Gm. per hundred cubic centimeters of blood.

A stillborn baby was delivered a few hours after admission. The following day the patient's condition was critical. The renal output was small. There were some edema of the extremities at this time and extensive edema of the face. During the patient's stay in the hospital the blood pressure varied markedly from time to time from a low level of 90 systolic and 30 diastolic to a high level of 180 systolic and 110 diastolic. Fever was constantly present, and the temperature varied from 101 to 108 F. Clinical signs of bronchopneumonia developed on the day preceding death.

The fluid intake and output and the quantity of sucrose and magnesium sulfate that this patient was given during hospitalization are tabulated as follows:

Duration of Medication	Fluid Intake, Cc.	Fluid Output, Cc.	Sucrose, 25 per Cent Solution, Cc.	Other Dehydrating Medication
1 day.....	850	450	50	20 cc. 20 per cent magnesium sulfate, I.V.
2 days.....	300	250	1,500	6 oz. saturated solution of magnesium sulfate, stomach tube
3 days.....	2,000	300	600	
4 days.....	3,000	300	.....	
5 days.....	3,240	250	.....	20 cc. 50 per cent magnesium sulfate, I.M.
6 days.....	1,650	250	.....	
7 days.....	3,050	700	300	
8 days.....	3,000	420	.....	
9 days.....	2,000	300	.....	
10 days.....	1,550	.....	.....	
Total.....	20,640	3,220+	2,450	

The anatomic diagnosis was as follows: eclampsia and spontaneous delivery; puerperal infection and extensive necrosis of the cervix and the uterine mucosa (a smear of material from the uterus showed *Bacillus welchii*, *Bacillus coli*, *Staphylococcus aureus* and a nonhemolytic streptococcus); fresh thrombi in the blood vessels and the wall of the uterus and in the broad ligament; embolic abscesses in the lungs; acute fibrinous pleurisy in the left lung; focal areas of necrosis in the mucosa of the colon; petechiae in the mucosa of the duodenum; an acute ulcer in the duodenum (traumatic?); hydropic degeneration of the epithelial cells of the kidneys (due to sucrose); decubitus ulcers over the skin of the body; surgical incisions over blood vessels in several areas of the body, and septicemia (causative organisms, *Staph. aureus* and a nonhemolytic streptococcus).

Essentially every epithelial cell in the convoluted portion of the tubules was swollen, and the cytoplasm was foamy. The lumens of the tubules were occluded. A small amount of albumin was present in some of Bowman's spaces. Hyaline droplets were present in the cytoplasm of some of the tubular epithelial cells. There were no significant changes in the glomeruli.

It is difficult to determine the role that each of the several disease processes may have played in this patient. It may be said, however, that the function of

the kidneys was abnormal on admission, as shown by the specific gravity of the urine and the excessive excretion of albumin. The effect of the bacterial infection would certainly help to lower the renal reserve. It is of interest to observe the small fluid output and the large intake beginning on the third day. Swelling of the epithelial cells, as a result of the injection of the sucrose on the first and the second day of hospitalization, may have been sufficient to reduce the renal output. Edema became more extensive during hospitalization.

CASE 11.—A Negress aged 8 gave a history of headache, stiffness of the neck and paralysis of the right side of the body of one week's duration and paralysis of the left side of two days' duration. She had been unable to swallow any food during the past four days and was unable to talk at the time of admission. The spinal fluid showed a trace of sugar and contained 660 mg. of chlorides per hundred cubic centimeters. There were 250 white cells per cubic centimeter of spinal fluid. These were primarily lymphocytes. Cultures of the spinal fluid were sterile. The white cell count was 6,500; the red cell count was 3,050,000, and the hemoglobin content was 10 Gm. per hundred cubic centimeters. The urine was normal. The patient died three days after admission to the hospital. The diagnosis was tuberculous meningitis.

This patient was given sucrose intravenously, and a series of determinations of the nonprotein nitrogen were made. The following data show the amount of fluid the patient received during the period of observation and the nonprotein nitrogen content of the blood at frequent intervals:

Date	Hour	Course of Illness	Administration of Fluids			Nonprotein Nitrogen in Blood, Mg. per 100 Cc.
			Fluid	Amount	Method	
9/15/40	.....	.....	Milk, fruit juice	960 cc.	Levin tube	..
			5% solution of dextrose	2,000 cc.		
9/16/40	.....	.....	5% solution of dextrose	1,000 cc.	.....	..
			Milk, fruit juice	640 cc.		
	2:15 p.m.	.....	25% solution of sucrose	100 cc.	Intravenous injection	27
	4:30 p.m.	.....	Orange juice	240 cc.	.....	..
	4:45 p.m.	.....	5% solution of dextrose	1,000 cc.	Intravenous injection	..
	8:00 p.m.	.....	Water	6 oz.	Levin tube	31
9/17/40	7:30 a.m.	.....	5% solution of dextrose	2,000 cc.	Intravenous injection	24
			Fruit juice, milk	220 cc.	Levin tube	
			Water	5 oz.	Levin tube	
9/18/40	7:30 a.m.	.....	Milk, fruit juice	720 cc.	Levin tube	..
	5:25 p.m.	Death				

The amount of sucrose given to this child was only half the quantity that produced renal lesions in some of the adults included in this series. There was no evidence of renal injury either before or after the injection of sucrose. The fluid intake apparently was adequate.

CASE 12.—A Negress aged 27 gave a history of headache of nine days' duration. The spinal fluid pressure was increased. There were 600 white cells, with 92 per cent lymphocytes, per cubic centimeter of spinal fluid. The fluid contained 30 mg. of sugar, 680 mg. of chlorides and 82 mg. of total protein per hundred cubic centimeters. The white cell count was 19,000 and the red cell count only 3,220,000. The urine was normal. A diagnosis of tuberculous meningitis was made. The

patient was given sucrose for its possible effect on the retention of nonprotein nitrogen in the blood. The following data show the quantity of fluids given:

Date	Hour	Course of Illness	Administration of Fluids			Nonprotein Nitrogen in Blood, Mg. per 100 Cc.
			Fluid	Amount, Cc.	Method	
9/14/40	.....	.....	10% solution of dextrose	1,000	.....	..
9/15/40	1:25 p.m.	.....	25% solution of sucrose	100	Intravenous injection	..
	1:35 p.m.	.....	10% solution of dextrose	1,000	Intravenous injection	..
9/16/40	9:50 a.m.	.....	10% solution of glucose	1,000	Intravenous injection	..
	2:30 p.m.	.....	25% solution of sucrose	100	Intravenous injection	23
	8:00 p.m.	.....	.....	.....	.....	33
9/17/40	8:00 a.m.	.....	10% solution of dextrose	1,000	Intravenous injection	33
9/18/40	8:00 a.m.	.....	.....	.....	.....	24
9/19/40	.....	.....	Liquids	.....	Oral administration	.
9/20/40	.....	.....	Liquids	.....	Oral administration	..
9/21/40	.....	.....	.....	.....	.....	25
	8:00 a.m.	.....	.....	.....	.....	28
9/27/40	.....	Death				

The quantity of fluid that this patient received during medication with sucrose was apparently adequate. There was no evidence of renal insufficiency either before or after the injection of sucrose. Each injection of sucrose given to this patient was only half that given to other adults in this series in whom tubular lesions developed.

CASE 13.—A white man aged 38 gave a history of a severe headache of two weeks' duration. The patient was semicomatose, mentally confused and extremely dehydrated. He was given 200 cc. of a 50 per cent solution of sucrose and within twenty minutes was able to answer questions intelligently.

There were signs of increased intracranial pressure. A diagnosis of either a brain tumor or a brain abscess was made. On the day following admission he was given 50 cc. of a 50 per cent solution of sucrose at 3:30 p. m. and a second injection of 200 cc. at 10 p. m. A cerebral abscess caused by *Pneumococcus* type III was drained on the third day of his stay in the hospital. On this same day he was given 200 cc. of a 50 per cent solution of sucrose, and an additional 100 cc. of sucrose solution was administered on the fourth day of hospitalization.

On the third and the fourth day of hospitalization he was also given 200 cc. of a 50 per cent solution of dextrose and 900 cc. of a 10 per cent solution of dextrose. Antipneumococcus serum, sulfamethylthiazole (2-[paraaminobenzenesulfonamido]-4-methylthiazole) and sodium sulfapyridine (the sodium salt of 2-[paraaminobenzenesulfonamido]-pyridine) were given after the evacuation of the abscess. Fluids were not forced because of the patient's condition. The fluid intake apparently reached its low point, 1,204 cc., on the fourth day of hospitalization. The patient died on the fifth day of hospitalization.

Essentially every epithelial cell lining the convoluted portion of the renal tubules was swollen. The cytoplasm was foamy. Some of these cells showed a greater

swelling than did others in corresponding portions of the tubules. There were a few scars in the kidney.

The patient was dehydrated at the time he was given the first injection of sucrose. A hypertonic solution of sucrose was administered on each day of hospitalization. Death occurred on the fifth day. The renal lesions were similar to those observed in rabbits given sucrose during a period of restricted fluid intake.

CASE 14.—A white woman aged 48 gave a history and presented the physical signs of an acoustic nerve tumor. At operation a large tumor was found and was resected piecemeal. The postoperative course was good until the third day. At this time the pulse and respirations became rapid and irregular. It was considered likely that some edema had developed in the region of the medulla and cerebellum. An intravenous injection of 200 cc. of a 50 per cent solution of sucrose was given at this time. The patient died eighteen hours later.

The patient was given several blood transfusions and an average daily injection of 1,500 cc. of saline solution.

Apparently every epithelial cell in the convoluted portion of the renal tubules was swollen. The cytoplasm was granular. Frequently these granules in the cytoplasm were widely separated by clear spaces. The lumens of the tubules were decreased in size, and some precipitated albumin was present in the tubules and in Bowman's spaces.

The renal lesions may be confused in this case with those of advanced cloudy swelling; however, they are consistent with the changes that occur in the rabbit after the injection of sucrose. Lesions such as these apparently represent a "physiologic-pathologic" process in a cell that may readily revert to normal function.

CASE 15.—A Negro aged 25 gave a history of headaches and convulsive seizures during the past five years. A diagnosis of an intracranial neoplasm was made, and at operation a large parasagittal meningioma was removed.

The patient was given several transfusions immediately after the operation. Frequent injections of solutions of dextrose in concentrations of 5 and 10 per cent were given intravenously. The fluid intake appears to have been adequate, especially during the later days of life.

Thirteen days after operation the patient was given 100 cc. of a 50 per cent solution of sucrose intravenously. On the twenty-third day after operation he was given 200 cc. of a 50 per cent solution of sucrose intravenously. Death occurred on the twenty-fourth day after operation and the first day after the second injection of sucrose.

Necropsy showed some precipitated albumin in the interstitial tissue in the area of the medulla of the kidney. Small collections of polymorphonuclear leukocytes were also present in the interstitial tissue. The epithelial cells of the tubules were greatly swollen, and their cytoplasm was foamy. The cytoplasm of some of these epithelial cells was homogeneous and stained deeply with eosin. The nuclei of many of the epithelial cells in the convoluted portion of the tubules were pyknotic, shrunken or absent. Some of the epithelial cells lining Bowman's spaces were swollen, and the cytoplasm was foamy. It was of interest to note that some of the epithelial cells in the convoluted portion of the tubules were apparently smaller than normal and stained more deeply with hematoxylin. These cells suggested those described in other cases as regenerative cells and did not show changes similar to those observed in the other tubules. Albumin, casts and occasional red and white blood cells were present in the lumens of the tubules. The glomeruli were frequently swollen.



The renal lesions were consistent with those that may occur after the injection of large quantities of sucrose.

CASE 16.—A white man aged 29 gave a history of chronic sinusitis with severe headache during the past month. After the patient's admission to the hospital signs of a brain abscess developed. At operation the abscess was drained. On the fifth day after operation the patient suddenly became comatose, the temperature rose to 39.3 C. (102.8 F.) and the respirations became rapid and shallow. An opening was made with a trephine over the midfrontal parietal region for the purpose of drainage. The patient died three hours after this operation.

On the day of death the patient was given 200 cc. of a 50 per cent solution of sucrose at 1:30 a. m. and a second injection of 200 cc. at 10:30 a. m. Death occurred at 2:20 p. m. He was given large amounts of dextrose solution in concentrations of 5 and 10 per cent for purposes of combating dehydration. Staphylococcus antitoxin was also given. He received one transfusion of 500 cc. of blood, without a reaction.

Essentially every epithelial cell lining the convoluted portion of the renal tubules was swollen, and the cytoplasm was foamy. Albuminous precipitate was present in the lumens of many of the tubules and in some of the spaces of Bowman.

The intake of fluid apparently was adequate. The patient was not appreciably dehydrated at any time. The renal lesions were similar to those that may occur after the injection of sucrose in experimental animals.

#### EXPERIMENTAL STUDY

Renal lesions have been produced in rabbits by Helmholz<sup>13</sup> and in dogs by Lindberg, Wald and Barker.<sup>14</sup> The quantity of sucrose administered and the length of time during which the animals were treated varied. Helmholz gave 1 rabbit 3,025 cc. of a 20 per cent solution of sucrose in twenty-one injections over a period of one hundred and eighty-two days. On the day after the last injection the blood contained 116 mg. of urea per hundred cubic centimeters and the excretion of phenol-sulfonphthalein was only 5 per cent in two hours. The rabbit was weak and was killed. Focal nephritis was present. The author stated: "The protoplasm of the cells of the convoluted tubules was finely granular and the cells were swollen so as to occlude the lumens of a few of the tubules."

Lindberg and associates<sup>14</sup> gave 100 cc. of a 50 per cent solution of sucrose intravenously to dogs each day for as long as fourteen days. For 1 of these animals, treated for ten days, the microscopic diagnosis was as follows: "Few glomeruli showed retrogressive changes; some hemorrhages into glomerular tufts and changes; early degeneration of convoluted tubules." They described the kidneys from a second dog treated in the same way: "The tubules essentially normal; no marked changes seen in glomeruli." For the kidneys from a third dog given one injection of sucrose and killed twenty-four hours later the following description was given: "Moderate hyperemia of glomerular tuft; proximal and distal convoluted tubules showed intense swelling nearly obstructing tubules; glomeruli were swollen and hemorrhagic."

This wide variation in the susceptibility of dogs and rabbits to the intravenous injection of sucrose is very likely similar to the variations in the frequency of the occurrence of renal lesions in man following the intravenous injection of a hypertonic solution of sucrose. The clinical data suggest that the development of the tubular changes may be influenced by the state of hydration before and during the time sucrose is given. Apparently the factor of "hydration" has not been considered in the experimental production of renal lesions by the injection of sucrose. The experimental study reported here was made to determine the effect of restriction of fluid on the development of renal lesions when a hypertonic solution of sucrose is given intravenously.

*Method and Material.*—Normal rabbits, weighing 1.5 to 3.0 Kg. each, were used. A 50 per cent solution of sucrose<sup>16</sup> was injected into the marginal veins of the ear in various quantities and at different times and intervals. Blood for the determination of nonprotein nitrogen<sup>17</sup> was taken from the heart. Frequent observations were made on the animals' weight.

The rabbits were fed cabbages, oats and water. In those experiments in which the fluid was restricted only oats were fed.

The rabbits were killed at various intervals. The kidneys were removed and fixed immediately in a 10 per cent concentration of solution of formaldehyde U. S. P. A complete autopsy was performed on some of the animals. Material for sectioning was embedded in paraffin, and the sections were stained with hematoxylin and eosin.

EXPERIMENT 1.—A group of 8 rabbits were given various quantities of sucrose, as shown in table 1. Two animals in this group which died within the first twenty-four hours are not included in the table. The intervals during which fluid was restricted were only twenty-four to forty-eight hours. There is some indication, however, from these data that restriction of fluids may affect the retention of the nonprotein nitrogen.

Rabbit 97 on the day before death was drowsy and inactive. No muscular twitching or convulsions were observed. This animal refused water on the morning before his death in the afternoon. At autopsy the kidneys were swollen and pale. The epithelial cells in the convoluted tubules were swollen, and the lumens were essentially occluded as a result of this swelling. There was little abnormal to be seen in the cytoplasm of the epithelial cells. A few pink threads of fibrin-like material were present. The nuclei were pyknotic, with irregular peripheries. No changes were observed in the glomeruli. Precipitated albumin-like material was present in Bowman's space in some of the glomeruli.

EXPERIMENT 2.—In a second group, of 18 rabbits, cabbage and water were removed from the diet for a much longer time before and during the period the sucrose was given. Table 2 shows the intervals during which the rabbits were given only oats and the quantity of sucrose administered to each animal. This table also gives the amount of nonprotein nitrogen in the blood. Each of the 6 rabbits (116, 117, 118, 122, 123 and 124) given only oats for four days before

16. Eli Lilly & Co. supplied the sucrose used in these experiments.

17. Mrs. R. L. Wyatt, technician in the chemistry laboratory of the Division of Medicine, determined the nonprotein nitrogen in the blood.

# Rabbit

Duration of  
Experiment,  
Day

	96	97	98	S-1	S-2	S-3
1.....	11:05 a.m. 15 cc. 4:00 p.m. 54 mg.	11:05 a.m. 15 cc. 4:00 p.m. 53 mg.	10:45 a.m. 34 Mg. 10:45 a.m. 15 cc. 1:30 p.m. 15 cc. 4:15 p.m. 34 mg.	9:00 a.m. 37 mg. 9:00 a.m. 20 cc. 11:15 a.m. 10 cc. 3:30 p.m. 20 cc. 10:00 a.m. 45 mg.	9:00 a.m. 46 mg. 9:00 a.m. 20 cc. 11:15 a.m. 10 cc. 3:30 p.m. 20 cc. 10:00 a.m. 54 mg.	9:00 a.m. 42 mg. 9:00 a.m. 20 cc. 11:15 a.m. 10 cc. 3:30 p.m. 20 cc. 10:00 a.m. 55 mg.
2.....	.....	.....	9:30 a.m. 20 cc. 1:15 p.m. 20 cc. 3:45 p.m. 35 mg.	10:00 a.m. 45 mg.	10:00 a.m. 54 mg.	10:00 a.m. 55 mg.
3.....	.....	.....	.....	8:00 a.m. 30 mg.	8:00 a.m. 32 mg.	10:00 a.m. 55 mg.
4.....	10:30 a.m. 38 mg. 10:30 a.m. 15 cc.	10:30 a.m. 46 mg. 10:30 a.m. 15 cc.	.....	9:30 a.m. 20 cc. 10:45 a.m. 20 cc. 11:30 a.m. 20 cc.	9:30 a.m. 20 cc. 10:45 a.m. 20 cc. 11:30 a.m. 20 cc.	9:30 a.m. 20 cc. 10:45 a.m. 20 cc. 11:30 a.m. 20 cc.
5.....	9:30 a.m. 15 cc. 1:15 p.m. 20 cc. 3:35 p.m. 28 mg.	9:30 a.m. 20 cc. 1:15 p.m. 20 cc. 3:45 p.m. 29 mg.	9:00 a.m. 20 cc.† 11:30 a.m. 20 cc. 1:30 p.m. 20 cc. 4:00 p.m. 45 mg.	.....	.....	.....
6.....	.....	.....	10:00 a.m. 45 mg.	8:15 a.m. 47 mg.	8:15 a.m. 34 mg.	8:15 a.m. 39 mg.
7.....	.....	.....	.....	8:00 a.m. 53 mg.	8:00 a.m. 54 mg.	8:00 a.m. 50 mg.
8.....	9:00 a.m. 30 cc. 11:30 a.m. 30 cc. 1:30 p.m. 30 cc. 4:00 p.m. 52 mg. Killed	9:00 a.m. 20 cc.† 11:30 a.m. 20 cc. 1:30 p.m. 20 cc. 4:00 p.m. 200 mg.	9:00 a.m. 187 mg.	8:30 a.m. 20 cc. 10:00 a.m. 20 cc.	8:30 a.m. 20 cc.† 10:00 a.m. 20 cc.	8:30 a.m. 10 cc.† 10:00 a.m. 20 cc.
9.....	.....	10:00 a.m. 353 mg. 4:30 p.m. Died	9:00 a.m. 260 mg.	8:00 a.m. 64 mg.	8:00 a.m. 43 mg.	8:00 a.m. 37 mg.
10.....	.....	.....	9:00 a.m. 176 mg.	8:15 a.m. 54 mg.	8:00 a.m. 88 mg.	8:15 a.m. 28 mg.
11.....	.....	.....	9:00 a.m. 143 mg.	8:00 a.m. 45 mg.	8:00 a.m. 45 mg.	8:00 a.m. 27 mg.
12.....	.....	.....	9:00 a.m. 88 mg.	.....	.....	.....
13.....	.....	.....	9:00 a.m. 66 mg.	.....	8:00 a.m. 34 mg.	8:00 a.m. 28 mg.
14.....	.....	.....	.....	9:30 a.m. 20 cc.† 11:00 a.m. 20 cc. 1:30 p.m. 20 cc. 4:00 p.m. 32 cc.	9:30 a.m. 20 cc.† 11:00 a.m. 20 cc. 4:00 p.m. 36 mg.	4:00 p.m. 47 mg.†
15.....	.....	.....	9:00 a.m. 44 mg.	9:00 a.m. 51 mg.	9:00 a.m. 41 mg.	9:00 a.m. 47 mg.
16.....	.....	.....	9:00 a.m. 55 mg.	9:00 a.m. 31 mg.	9:00 a.m. 43 mg.	9:00 a.m. 28 mg.
17.....	.....	.....	8:00 a.m. Died	.....	.....	.....
22.....	.....	.....	.....	8:30 a.m. 60 cc.†	8:30 a.m. 60 cc.†	8:30 a.m. 60 cc.†
23.....	.....	.....	.....	8:30 a.m. 33 mg.†	8:30 a.m. 30 mg.†	8:30 a.m. 40 mg.†
24.....	.....	.....	.....	8:30 a.m. 33 mg.	8:30 a.m. 34 mg.	8:30 a.m. 26 mg.
28.....	.....	.....	.....	9:30 a.m. 20 cc.† 1:30 p.m. 20 cc. 4:00 p.m. 20 cc.	9:30 a.m. 20 cc.† 1:30 p.m. 20 cc. 4:00 p.m. 20 cc.	9:30 a.m. 20 cc.† 1:30 p.m. 20 cc. 4:00 p.m. 20 cc.
29.....	.....	.....	.....	8:00 a.m. 32 mg.	8:00 a.m. 38 mg.	8:00 a.m. 97 mg.
30.....	.....	.....	.....	8:00 a.m. 43 mg. Experiment discontinued	8:00 a.m. 38 mg. Experiment discontinued	8:00 a.m. 36 mg. Experiment discontinued

TABLE 2.—Effect of Restriction of Fluids on Retention of Nonprotein Nitrogen in Rabbits Given Sucrose \*

Diet	Rabbit	Duration of Experiment, Days									
		1	2	3	4	5	6	7	8	9	10
Only oats for 3 days before and during experiment	110†	3:30 p.m.† 55 mg.	.....	.....	.....	.....	.....	..	.....	.....	.....
	111	3:30 p.m.† 123 mg.	.....	.....	.....	.....	.....	..	.....	.....	.....
	112	3:30 p.m.† 43 mg.	.....	.....	.....	.....	.....	..	.....	.....	.....
	113	3:30 p.m.† 43 mg.	.....	.....	.....	.....	.....	..	.....	.....	.....
Oats, water and cabbage for 3 days before and during experiment	114	3:30 p.m.†	.....	.....	.....	.....	.....	..	.....	.....	.....
	115	3:30 p.m.†	.....	.....	.....	.....	.....	..	.....	.....	.....
	116	9:30 a.m. 20 cc.	9:00 a.m. 20 cc.	10:00 a.m. 20 cc.	9 a.m. 20 cc. 5 p.m. 120 mg.	4:00 p.m. 1:30 mg.	.....	..	3:00 p.m. 316 mg.	5:00 p.m.† 420 mg.	.....
	117	9:30 a.m. 20 cc.	9:00 a.m. 20 cc.	10:00 a.m. 20 cc.	9 a.m. 20 cc. 5 p.m. 154 mg.	4:00 p.m. 65 mg.	.....	..	3:00 p.m.† 375 mg.	.....	.....
Only oats for 4 days before and during experiment	118	9:30 a.m. 20 cc.	9:00 a.m. 20 cc.	10:00 a.m. 20 cc.	9 a.m. 20 cc. 5 p.m. 139 mg.	.....	.....	..	.....	.....	.....
	119	9:30 a.m. 20 cc.	9:00 a.m. 20 cc.	10:00 a.m.† 38 mg.	.....	.....	.....	..	.....	.....	.....
	120	9:30 a.m. 20 cc.	9:00 a.m. 20 cc.	10:00 a.m. 20 cc.	9:00 a.m. 20 cc.	4:00 p.m. 67 mg.	.....	..	3:00 p.m. 38 mg.	.....	9:00 a.m.† 30 mg.
	121	9:30 a.m. 20 cc.	9:00 a.m. 20 cc.	10:00 a.m. 20 cc.	9:00 a.m. 20 cc.	4:00 p.m. 75 mg.	.....	..	3:00 p.m. 40 mg.	.....	9:00 a.m.† 34 mg.
Only oats for 4 days before and during experiment	122	9:00 a.m. 36 mg.	9:00 a.m. 20 cc.	9 a.m. 54 mg.† 9 a.m. 20 cc.	.....	.....	.....	..	.....	.....	.....
	123	9:00 a.m. 50 mg.	9:00 a.m. 20 cc.	9 a.m. 50 mg. 9 a.m. 64 mg.	.....	9:00 a.m. 200 mg.	.....	..	4:00 p.m.† 214 mg.	.....	.....
	124	9:00 a.m. 34 mg.	9:00 a.m. 20 cc.	9 a.m. 82 mg. 9 a.m. 53 mg.	3:00 p.m. 20 cc.	9:00 a.m. 88 mg.	4:00 p.m.† 100 mg.	..	.....	.....	.....
	125	9:00 a.m. 54 mg.	9:00 a.m. 20 cc.	9 a.m. 49 mg. 9 a.m. 20 cc.	3:00 p.m. 20 cc.	9:00 a.m. 30 mg.	Experiment discontinued	..	.....	.....	.....
Only oats for 4 days before experiment; cabbage added when sucrose was first injected	126	9:00 a.m. 20 cc.	9:00 a.m. 20 cc.	9 a.m. 42 mg. 9 a.m. 41 mg.	3:00 p.m. 20 cc.	9:00 a.m. 39 mg.	4:00 p.m. 36 mg.	..	.....	.....	.....
	127	.....	.....	9 a.m. 41 mg. 9 a.m. 20 cc.	3:00 p.m. 20 cc.	9:00 a.m. 30 mg.	4:00 p.m.† 55 mg.	..	.....	.....	.....
	128	9:00 a.m. 50 mg.	9:00 a.m. 51 mg.	.....	.....	9:00 a.m. 53 mg.	Experiment discontinued	..	.....	.....	.....
	129	.....	9:00 a.m. 67 mg.	.....	.....	9:00 a.m. 68 mg.	Experiment discontinued	..	.....	.....	.....

\* All measurements in cubic centimeters refer to intravenous injection of a 50 per cent solution of sucrose, and all those in milligrams signify the amount of nonprotein nitrogen per hundred cubic centimeters of blood.  
† Rabbits 110 to 115 were given 15 cc. of sucrose solution at 10 a.m. and at 1 p.m. and were killed at 3:30 p.m.  
‡ Killed.

the sucrose was injected showed a retention of nonprotein nitrogen either after the third or after the fourth injection. The controls (rabbits 119, 120, 121, 125, 126 and 127) did not exhibit a corresponding retention of nonprotein nitrogen. In fact, there was only a slight retention of nonprotein nitrogen by rabbits 120 and 121, and in the others this factor was normal.

Two rabbits (128 and 129), as shown in table 2, were given only oats for four days, and the nonprotein nitrogen in their blood was determined on the fourth, the fifth and the seventh day. It was only slightly elevated.

The rabbits given only oats and sucrose rapidly lost weight. Those given oats, cabbage and water during the time sucrose was injected showed insignificant variations in weight. In fact, some of the animals gained. Rabbits given only

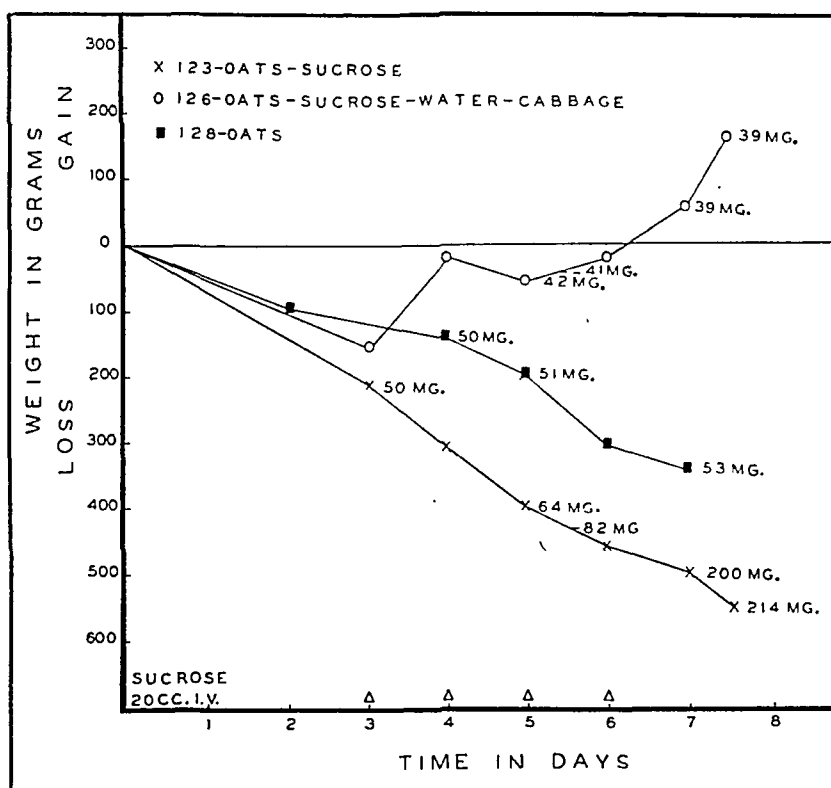


Fig. 1.—The effect of sucrose on the weight of rabbits and their retention of nonprotein nitrogen when the fluid intake is restricted.

oats lost weight; however, this was much less than when sucrose was also given. The variations in the weight of the different groups of rabbits are illustrated by the data in figure 1.

The kidneys in rabbits 110, 111, 112, 113, 114 and 115 showed essentially the same degree of tubular injury. The cells in the convoluted portion of the renal tubules were slightly swollen, and the cytoplasm was finely granular. The kidneys from rabbits 116, 117, 118, 122 and 123 showed the cells in the convoluted portion of the tubules to be greatly swollen, the cytoplasm vacuolated and the nuclei pyknotic. The lumens of the tubules were frequently occluded. Precipitated albuminous material was present in Bowman's space in some of the glomeruli and in the lumen in some of the tubules. No lesions were observed in the glomeruli, in Henle's loops or in the collecting tubules. The renal changes in rabbits 119,

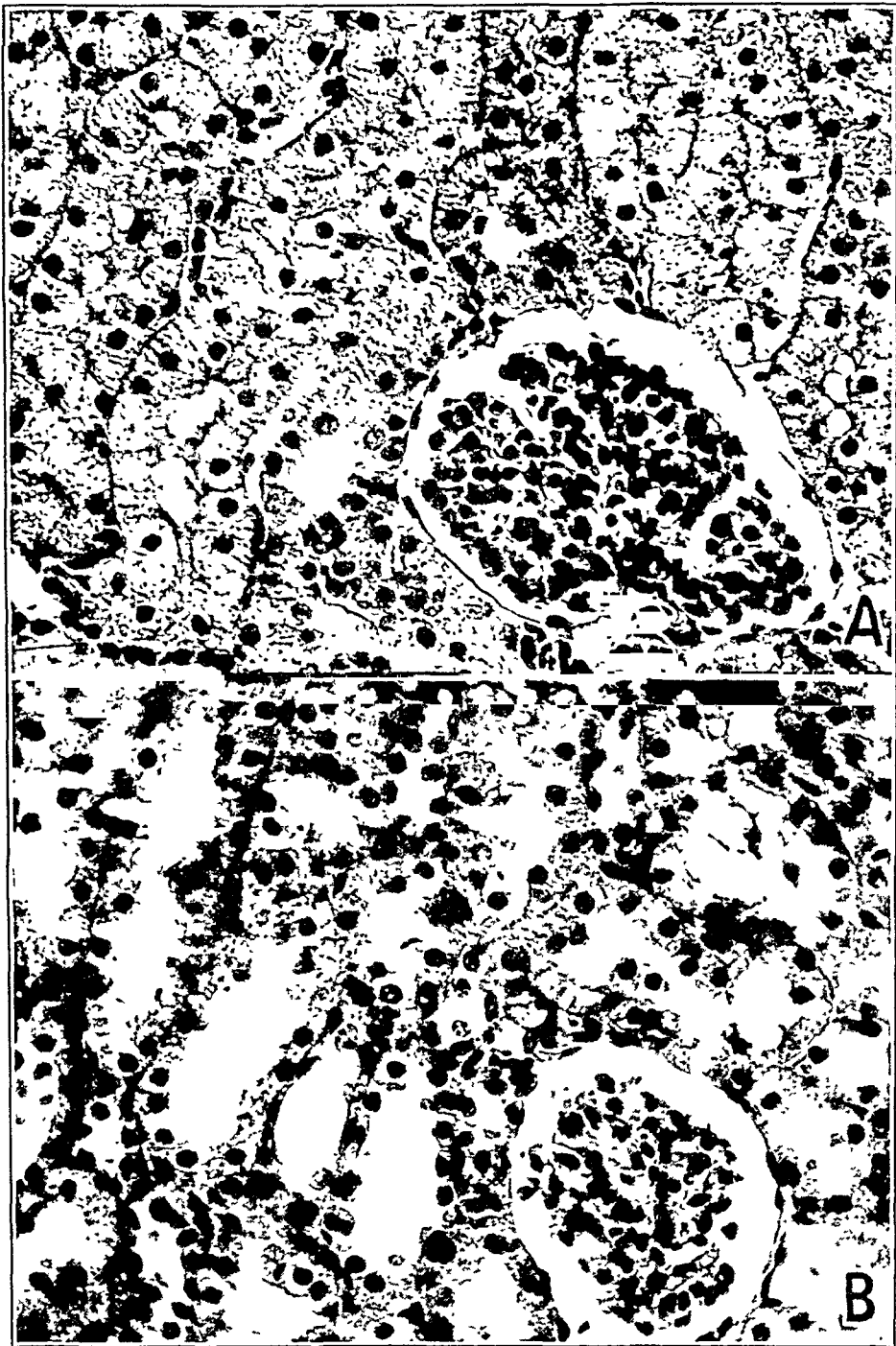


Fig. 2.—*A* (rabbit 118), the lumens of tubules almost occluded by the greatly swollen epithelial cells. This rabbit was fed only oats for four days before and during the experiment. Twenty cubic centimeters of a 50 per cent solution of sucrose was injected intravenously each day for four days. Eight hours after the last injection the blood contained 139 mg. of nonprotein nitrogen per hundred cubic centimeters. The rabbit was killed on the fourth day of the experiment. *B* (rabbit 121), normal appearance of the kidneys. This rabbit was fed oats, cabbage and water for four days before and during the experiment. It was given the same amount of sucrose as was administered to rabbit 118. At the time rabbit 121 was killed, six days after the last injection of sucrose, the blood contained 34 mg. of nonprotein nitrogen per hundred cubic centimeters.

126 and 127 were similar to those in rabbit 110. It would appear that the lesion in the epithelial cells of the tubules in this group of rabbits varies only in degree from that in the rabbits given sucrose and fed oats, water and cabbage.

The degree of the pathologic change in the kidney of rabbit 124 appears to be about midway between that of rabbit 127 and rabbit 123. The nonprotein nitrogen value for rabbit 124 was 100 mg. per hundred cubic centimeters of blood, while that for rabbit 123 was 214 mg. and that for rabbit 127 was 55 mg.

There were no pathologic changes in the epithelial cells of the convoluted portion of the renal tubules in rabbits 120 and 121. The nonprotein nitrogen was also normal. It is important to observe in table 2 that the nonprotein nitrogen values for these 2 animals were 67 and 75 mg., respectively, per hundred cubic centimeters on the fifth day of the experiment. On the tenth day, when the animals were killed, the values were normal.

There were no pathologic changes in the other viscera of these animals that we can at present associate with the administration of sucrose.

EXPERIMENT 3.—Of a group of 5 rabbits, 2 were fed oats, cabbage and water and 3 were fed only oats. On the fourth day of the experiment each rabbit was given 25 cc. of a 50 per cent solution of sucrose. This injection of sucrose was repeated on the four following days. On the day following the last injection of sucrose the nonprotein nitrogen in the blood of the 2 rabbits given cabbages, oats and water was within the range of normal, while each of the other animals showed a retention of nonprotein nitrogen in the blood.

#### COMMENT

The quantity of sucrose given to the patients in cases 1, 3 and 7 was much less than that given to patients by Dyar and Matthew<sup>7</sup> and by Masserman.<sup>8</sup> Renal lesions were present in each of our patients. The investigators just mentioned failed to observe any "unfavorable" reactions in their patients, although a larger quantity of sucrose was injected by the same route. Anderson<sup>13</sup> concluded from his studies that previous renal lesions influenced the development of tubular lesions following the injection of sucrose. Murphy and his associates<sup>2</sup> gave 300 to 500 cc. of a 50 per cent solution of sucrose to a group of 21 patients with chronic hypertension and observed improvement, without unfavorable results. It appears that previous renal disease, such as glomerular and arteriosclerotic nephritis, has little if any effect on the development of renal lesions following the injection of sucrose.

An insufficient amount of fluid apparently was given to some of our patients in whom tubular lesions developed after the injection of sucrose. In case 1 the patient was unconscious for approximately forty-eight hours before he was admitted to the hospital. He was given 200 cc. of a 25 per cent solution of sucrose one hour after admission and died three hours later. This case illustrates the rapidity with which this tubular lesion may develop. This has been discussed by Anderson.<sup>13</sup> The quantity of fluid given in case 10 after the third day apparently was adequate. The fluid output was low. It would seem that the epithelial

cells lining the convoluted tubules of the kidney may have become swollen on the second day after the injection of sucrose. The lumens of the tubules were blocked as a result of the swelling of these cells. Helmholtz<sup>11</sup> discussed the occlusion of the lumen of the tubules in rabbits given sucrose.

Our experimental observations on the rabbit show that in animals given sucrose but no fluid renal lesions develop and nonprotein nitrogen is retained in the blood. The quantity of sucrose necessary to produce renal lesions in dehydrated rabbits is much less than that used by Helmholtz<sup>11</sup> to produce renal lesions.

There are insufficient clinical data to indicate the effect of this renal lesion on renal function. The experimental results of Helmholtz<sup>11</sup> and Lindberg and associates,<sup>14</sup> as well as ours, show that the renal function is definitely diminished after the injection of sucrose.

A knowledge of the quantity of sucrose that will produce renal lesions is important. In cases 4 and 5 the patients were given 100 cc. each of a 25 per cent solution of sucrose intravenously. No renal lesions were present. It is difficult to determine the degree of hydration of these patients at the time sucrose was given. The patient in case 11 was a child 8 years old. She was given adequate fluids during the time she received the sucrose. There was no retention of nonprotein nitrogen. In case 12 the patient was given adequate fluids and two intravenous injections of 100 cc. each of a 25 per cent solution of sucrose. No retention of nonprotein nitrogen occurred. The pathologic studies on rabbits suggest that there is a definite correlation between the development of tubular lesions and the retention of nonprotein nitrogen in the blood.

Multiple injections of sucrose were given to a group of patients by Hilton and Alderson.<sup>3</sup> The total quantity, however, was much less than that given to several of the patients included in the present series. It seems unlikely that the occurrence of these renal lesions is directly influenced by a previous injection of sucrose. The chemical and pharmacologic action of sucrose has been discussed by Keith and Power,<sup>9</sup> Keith<sup>18</sup> and Bullock, Gregersen and Kinney.<sup>19</sup>

The pathologic lesions observed in our experimental animals and in the patients appear to be identical and to be similar to those reported by other investigators. We did not observe glomerular lesions like those described by Lindberg and his associates.<sup>14</sup> The results of the histologic studies and the observations on the retention of nonprotein nitrogen suggest a correlation between these pathologic changes and renal func-

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18. Keith, N. M.: Experimental Dehydration, *Am. J. Physiol.* **68**:80, 1924.

19. Bullock, L. T.; Gregersen, M. I., and Kinney, R.: The Use of Hyper-tonic Sucrose Solution Intravenously to Reduce Cerebrospinal Fluid Pressure Without a Secondary Rise, *Am. J. Physiol.* **112**:82, 1935.



tion. It is suggested from the studies on rabbits 120, 121, 126 and 127 that the epithelial changes in the tubules may be transient and that the quantity of sucrose is important in the production of the renal lesions.

This renal lesion was diffuse in all of the rabbits and in a majority of the patients. In some of the patients with arteriolosclerotic nephritis the epithelial cells lining the tubules were smaller than normal in focal areas of the kidney. Dr. R. A. Moore and Dr. W. D. Forbus discussed this factor when Anderson<sup>18</sup> presented his paper at a meeting of the Southern Medical Association. The epithelial cells lining the convoluted portion of the tubules in those cases in which the changes are focal are frequently much lower and stain more deeply with hematoxylin than do corresponding cells in normal kidneys. The appearance of these epithelial cells and their failure to respond to sucrose as do other tubular epithelial cells may be similar to the effect of uranium nitrate on previously injured tubular epithelial cells, observed by MacNider.<sup>20</sup>

#### SUMMARY

A group of 16 clinical cases in which a hypertonic solution of sucrose was given intravenously is reported. In some instances the epithelial cells in the convoluted portion of the renal tubules were swollen. From a review of these cases it appears that dehydration is one of the most important factors in determining whether or not this tubular lesion will occur after the intravenous injection of sucrose. The quantity of sucrose administered during a given interval is also important.

Renal lesions similar to those in man may be produced experimentally by giving rabbits sucrose intravenously. The quantity of sucrose necessary to produce these lesions is much less when the fluid is restricted before and during the experiment. In fact, when fluids are given it is difficult to produce renal lesions in rabbits with sucrose unless large quantities are used.

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20. MacNider, W. de B.: *Urine Formation During the Acute and Chronic Nephritis Induced by Uranium Nitrate*, in *Harvey Lectures, 1928-1929*, Baltimore, Williams & Wilkins Company, 1930, p. 82.

# Progress in Internal Medicine

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## LIVER AND BILIARY TRACT

A REVIEW FOR 1941

CARL H. GREENE, M.D.

NEW YORK

### FUNCTIONAL ACTIVITY OF THE COMMON BILE DUCT AND THE SPHINCTER OF ODDI

The physiology of the biliary tract was reviewed in 1937.<sup>1</sup> At that time the various factors chiefly affecting the flow of bile with especial reference to the secretory pressure of the liver, the contractility and storage function of the gallbladder, the resistance of the sphincter of Oddi and the effect of changes in duodenal tone and motility were discussed in some detail. The literature dealing with the sphincter mechanism of the common bile duct in human subjects has been comprehensively reviewed by Bergh.<sup>1a</sup> The recognition that the flow of bile through the various portions of the biliary tract is subject to physiologic control has had broad clinical implications, and an extensive clinical literature dealing with disturbances in this functional control has arisen in consequence. One of the most recent experimental analyses of the mechanics of the bile flow has been that of Necheles and Kozoll.<sup>2</sup> They took separate records of the contractions of the gallbladder and of the duodenum, of the tone of the sphincter of Oddi, of respiration and of the blood pressure. They found that the sphincter of Oddi in dogs possesses a regular and distinct tonus rhythm. This was entirely independent of the tonus of the gallbladder, and there was no definite

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From the Clinic for the Study of Disease of the Liver and Biliary Tract of the Department of Medicine and the Department of Surgery, New York Post-Graduate Medical School and Hospital, Columbia University.

1. Greene, C. H.; Handelsman, M. B., and Babey, S. M.: Liver and Biliary Tract: A Review for 1936, *Arch. Int. Med.* **59**:724 (April) 1937.

1a. Bergh, G. S.: The Sphincter Mechanism of the Common Bile Duct in Human Subjects: Its Reaction to Certain Types of Stimulation, *Surgery* **11**:299 (Feb.) 1942.

2. Necheles, H., and Kozoll, D. D.: A Study of the Sphincter of Oddi in the Human and in the Dog, *Am. J. Digest. Dis.* **9**:36 (Jan.) 1942. Kozoll, D. D., and Necheles, H.: A Study of the Mechanics of Bile Flow: I. Responses to Physiological Intravenous Solutions, *Surg., Gynec. & Obst.* **74**:27 (Jan.) 1942; II. Response to Intraduodenal Solutions, *ibid.* **74**:692 (March) 1942; III. Responses to Pharmacological Stimuli, *ibid.*, to be published.

correlation between the activity of the duodenum and that of the sphincter of Oddi. In many cases the sphincter of Oddi and the duodenal musculature showed the same type of response to stimulation or to drugs, but the responses were independent of each other.

Kozoll and Necheles report that the intravenous injection of physiologic or hypertonic solutions of sodium chloride induces spasm both of the sphincter and of the duodenum. Dextrose solutions, on the other hand, produced a relaxation of the duodenum, with slight or only moderate increase in the tone of the sphincter. Their studies were extended to include a group of patients with a T tube in the common bile duct. An extensive pharmacologic study showed that the response to drugs of the epinephrine group, i. e., epinephrine, ephedrine, epinine (dihydroxyphenylethylmethylaniline), propadrine hydrochloride and neosynephrin hydrochloride, was inconstant. Atropine reduced the sphincter tone or the response of the sphincter to saline solutions in the dog. When the drug was given to patients in doses sufficient to produce discomfort there was some increase in the resistance of the sphincter. The response to papaverine was inconstant. Morphine and codeine produced spasm of the sphincter. Glyceryl trinitrate, amyl nitrite and the hydrochloride of diphenylacetyl-diethylaminoethanol (trasentin) all reduced the tone of the sphincter and were able to cause relaxation after the administration of codeine. Prostigmine usually increased both the tone of the sphincter and the motility of the duodenum. Necheles and Kozoll and Bergh<sup>3</sup> found that a fatty meal of egg yolk and cream often caused a slight initial contraction of the sphincter. This was then followed by a relaxation for sometimes as long as two to three hours after the meal. Bergh found that olive oil was less effective in reducing the tone of the sphincter than were egg yolk and cream. Protein and carbohydrate meals were without significant effect on the tone of the sphincter.

Mirizzi was one of the pioneers in the development of the technic of cholangiography. He<sup>4</sup> has recently presented a summary of his experience with cholangiography and his views regarding functional disturbances of the sphincter of Oddi. He reports cholangiograms which he interprets as demonstrating spasm and the presence of peristaltic waves in the common duct. MacDonald<sup>5</sup> also reports a case in which he found cholangiographic evidence of peristalsis in the terminal portion of the common duct and the papilla of Vater. Carter and Maraffino<sup>6</sup> have observed a case in which a similar process was evident.

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3. Bergh, G. S.: The Effect of Food upon the Sphincter of Oddi in Human Subjects, *Am. J. Digest. Dis.* **9**:40 (Jan.) 1942.

4. Mirizzi, P. L.: Functional Disturbances of the Choledochus and Hepatic Bile Ducts, *Surg., Gynec. & Obst.* **74**:306 (Feb., no. 2A) 1942.

5. MacDonald, D.: Common Bile Duct Peristalsis: Preliminary Report, *Surg., Gynec. & Obst.* **73**:864 (Dec.) 1941.

6. Carter, R. F., and Maraffino, B.: Personal communication to the author.

Mirizzi stresses the frequency of functional spasm of the sphincter of Oddi and insists that such spasm is associated with hypertrophy of the sphincter that still further interferes with the free passage of bile. He also considers the reflux of contrast medium into the duct of Wirsung a characteristic pathologic finding in the presence of dystonia of the sphincter of Oddi. Such reflux into the pancreatic ducts he believes to be a frequent cause of anatomic changes in the pancreas. This view is not very different from those usually held in this country, though most authors would not be willing to admit that pancreatic reflux is necessarily evidence of spasm of the sphincter of Oddi.

#### ETIOLOGY OF GALLSTONES

The various theories regarding the etiology of stones in the gallbladder were reviewed in detail by Phemister and his associates<sup>7</sup> and by Carter, Greene, Twiss and Hotz.<sup>8</sup> The last-named authors pointed out that no single mechanism would explain the formation of all the various types of gallstones. Their experience emphasized the relative importance of biliary stasis as compared to infection. A new and original point of view has recently been presented by Martensson.<sup>9</sup> He noted that many gallstones contained a central nucleus of necrotic epithelial cells and that sporulating bacilli were found in the epithelial cell walls in some cases of chronic cholecystitis. Cultures of material from diseased gallbladders removed at operation or at necropsy commonly showed the presence of what the author described as a typical bacillus. This was a gram-positive, motile, endosporulating rod. Different strains varied, some being facultative, others being obligatory, anaerobes. The bacillus did not fit any previously described organism in all its characteristics. Martensson was able to produce gallstones experimentally in rabbits, pigs, sheep and cattle by intravesicle, intravenous, subcutaneous or oral administration of cultures of this organism. If rabbits were first immunized against the organism, then biliary calculi did not develop after the injection of cultures.

It has long been recognized that organisms of the type of *Bacillus welchii* or *Bacillus proteus vulgaris* can be grown with a fair degree of regularity from cultures of the liver, bile or wall of the gallbladder.

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7. Phemister, D. B.; Aronsohn, H. G., and Pepinsky, R.: Variations in the Cholesterol, Bile Pigment and Calcium Salts Contents of Gall Stones Formed in the Gall Bladder and in Bile Ducts with the Degree of Associated Obstruction, *Ann. Surg.* **109**:161 (Feb.) 1939.

8. Carter, R. F.; Greene, C. H.; Twiss, J. R., and Hotz, R.: Etiology of Gallstones: Critical Survey of the Literature and a Study of the Applicability of Various Theories in Two Hundred and Thirty-Nine Operative Cases, *Arch. Surg.* **39**:691 (Nov.) 1939.

9. Martensson, K.: Studies on the Etiology of Gallstones: A Subtilis-Like Bacilli-Group as an Etiologic Factor, *Acta chir. Scandinav.* **84**:227, 1941.

The culture and identification of the various anaerobic organisms require a careful and painstaking technic and so are not often done. The relation between this organism and the other anaerobic organisms described is still indeterminate. Without independent verification and further study this work cannot be accepted as conclusive, but it is most interesting and should stimulate further investigation.

#### GIARDIASIS AND THE BILIARY TRACT

*Giardia lamblia* is not an uncommon intestinal flagellate and often has been recognized in duodenal contents after drainage. It usually has been considered a harmless organism, and little attention has been paid to its presence. That it does enter the gallbladder is shown by the reports of a few cases<sup>10</sup> in which parasites were reported in bile obtained by aspiration from the gallbladder at operation or necropsy. The clinical significance of such infestation was undecided for a long time because of the absence of any effective method of treatment. The introduction by Galli-Valerio of atabrine in 1937<sup>11</sup> as a specific remedy for giardiasis has been amply confirmed by the reports of de Muro,<sup>12</sup> Morrison and Swalm,<sup>13</sup> Nutter, Rodaniche and Palmer<sup>14</sup> and Hartman and Kyser.<sup>15</sup> This treatment is effective in causing the disappearance of the flagellate both from the stool and from the material obtained by duodenal drainage. Many patients with giardiasis complain of moderate or intermittent diarrhea as well as mild digestive disturbances. After the eradication of the parasite the symptoms often disappear. These results therefore indicate that giardiasis are mildly pathogenic for man. Their significance in regard to the biliary tract per se is still undetermined, but in view of the effectiveness of atabrine therapy, this question is of minor significance.

10. Westphal, K., and Georgi: Ueber die Beziehungen der *Lambliia intestinalis* zu Erkrankungen der Gallenwege und Leber, München. med. Wchnschr. **70**:1080 (Aug. 17) 1923. Smithies, F.: Parasitosis of the Bile Passages and Gallbladder: A Report on Thirty-Seven Instances of Protozoiasis and One Instance of Infestation by *Necator Americanus*, Am. J. M. Sc. **176**:225 (Aug.) 1928. Calder, R. M., and Rigdon, R. H.: *Giardia* Infestation of Gallbladder and Intestinal Tract, *ibid.* **190**:82 (July) 1935. Hartman, H. R.; Kyser, F. A., and Comfort, M. W.: Infection of the Gallbladder by *Giardia Lamblia*, J. A. M. A. **118**:608 (Feb. 21) 1942.

11. Galli-Valerio, B.: La lamblia et son traitement par l'atébrine, Schweiz. med. Wchnschr. **67**:1181 (Dec. 11) 1937.

12. de Muro, P.: Atebrinbehandlung bei Giardiasis (Lamblia), Deutsche med. Wchnschr. **65**:262 (Feb. 17) 1939.

13. Morrison, L. M., and Swalm, W. A.: A New Effective Parasiticide in Giardiasis, Am. J. Digest. Dis. **6**:325 (July) 1939.

14. Nutter, P. B.; Rodaniche, E. C., and Palmer, W. L.: *Giardia Lamblia* Infection in Man, J. A. M. A. **116**:1631 (April 12) 1941.

15. Hartman, H. R., and Kyser, F. A.: Giardiasis and Its Treatment: A Clinical Study, J. A. M. A. **116**:2835 (June 28) 1941.

## CIRCULATION OF THE LIVER

The circulation of the liver is unique in that this organ receives both an arterial and a venous supply of blood. Their relative importance is still undetermined, though a subject of intensive study. Grindley, Herrick and Mann<sup>16</sup> measured the flow of blood to and from the liver in unanesthetized dogs. From these data Snyder<sup>17</sup> calculates that the blood flow in the hepatic artery is approximately one seventh of that in the portal vein.

The importance of the blood flow in the portal vein was indicated by the earlier observation that regeneration of the liver was not observed in animals with Eck fistulas. Higgins, Mann and Priestley<sup>18</sup> likewise found that regeneration after removal of a portion of the liver was not as active in birds as it was in mammals in which the whole of the portal blood flows through the liver. In his most recent experiments Mann<sup>19</sup> reports further evidence that the restoration of hepatic tissue after extirpation or injury depends almost completely on the supply of portal blood. The results of Grindley, Herrick and Mann showed considerable difference between the flow of blood to and from the liver, thus confirming older clinical impressions indicating the importance of the liver as a site for the storage of blood.

Numerous anatomic studies,<sup>20</sup> especially those of Pfuhl, Tischendorf, Arey and associates and Tyler, have served to establish the existence of mechanisms capable of distributing and regulating the flow of blood through the liver. In the hepatic veins and venules of the dog the smooth muscle cells are not evenly arranged in a continuous sheet as in ordinary veins but are grouped in spiral bands. At the opening of the hepatic venules into the hepatic veins, these bands are thickened and annular so as to provide sphincters. Similar annular sphincters are present at the openings of the hepatic veins into the inferior vena cava. Deysach<sup>21</sup>

16. Grindley, J. H.; Herrick, J. F., and Mann, F. C.: Measurement of the Blood Flow of the Liver, *Am. J. Physiol.* **132**:489 (March) 1941.

17. Snyder, C. D.: Recent Advances in Knowledge of the Liver, *Physiol. Rev.* **22**:54 (Jan.) 1942.

18. Higgins, G. M.; Mann, F. C., and Priestley, J. T.: Experimental Pathology of the Liver: X. Restoration of the Liver of the Domestic Fowl, *Arch. Path.* **14**:491 (Oct.) 1932.

19. Mann, F. C.: The Portal Circulation and Restoration of the Liver After Partial Removal, *Surgery* **8**:225 (Aug.) 1940.

20. Pfuhl, W.: Die Leber, in von Möllendorff, W.: *Handbuch der mikroskopischen Anatomie des Menschen*, Berlin, Julius Springer, 1932, vol. 5, pt. 2, p. 235. Tischendorf, F.: Histologische Beiträge zur Kenntnis der venösen Lebersperre, *Ztschr. f. mikr.-anat. Forsch.* **45**:266, 1939. Tyler, F. H.: A Note on the Microstructure of the Turtle's Liver, *Anat. Rec.* **79**:541 (April 25) 1941. Arey, L. B.; Sohlberg, R. J., and Rutherford, R. B.: Throttling Veins in the Livers of Certain Mammals, *ibid.* **81**:21 (Sept. 25) 1941.

21. Deysach, L. J.: Nature and Location of "Sphincter Mechanism" in Liver as Determined by Drug Actions and Vascular Injections, *Am. J. Physiol.* **132**:713 (April) 1941.

describes small endothelial tubes situated in the walls of the sublobular and central veins and connected with the veins through ostiums guarded by sphincters. Filling and emptying of these tubes by the action of the sphincters would provide a means of removing or adding considerable amounts of blood to the general circulation. The portal vessels differ from the hepatic venules in that they are devoid of smooth muscle.

These anatomic studies provide a mechanism for the regulation of the blood flow through the liver. Snyder and Tyler<sup>22</sup> summarize much of the evidence dealing with the different factors which affect that flow. Responses both to cholinergic, or vagal, and to adrenergic, or sympathetic, simulating agents are obtained but apparently are variable. These authors point out the numerous difficulties in the interpretation of results in studies of the hepatic blood flow, especially when a simultaneous study of the effect on the metabolic exchanges taking place in the liver is desired. Among other factors they emphasize the large amount of lymph formed in the liver and the effect of the resultant difference between the hepatic inflow and outflow.

Another method of observing certain phases of the hepatic circulation directly is reported by Wakim.<sup>23</sup> Using a method of transillumination, he was able to watch the circulation in the sinusoids and capillaries in frogs and rats. The circulation in the sinusoids was intermittent, with phases of activity alternating with periods of inactivity. During rest the sinusoids may be empty or may be packed with blood cells and apparently serve as storehouses. The hepatic artery was found to supply blood to the parenchyma through several routes. Some of the arterial terminals empty directly into the sinusoids. Other arterial branches empty into the portal vein proximal to the sinusoids. Direct arteriovenous anastomoses between the branches of the hepatic artery and the portal vein were also observed. It is possible that further work along this line will help increase the present day understanding of the intermittent or cyclic functions of the liver and the specific localization of the effects of some hepatic toxins.

Preliminary experiments on the latter problem are reported by Wakim and Mann.<sup>24</sup> They found that the inhalation of carbon tetrachloride produces an immediate vasoconstrictor effect on the circulation

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22. Snyder, C. D.: *Rev. Gastroenterol.*, to be published. Snyder, C. D., and Tyler, F. H.: *Metabolism Studies on Surviving Turtle's Liver*, *J. Cell. & Comp. Physiol.* **16**:377, 1940.

23. Wakim, K. G.: *The Intrahepatic Circulation of Blood in the Intact Animal: Preliminary Report*, *Proc. Staff Meet., Mayo Clin.* **16**:198 (March 26) 1941.

24. Wakim, K. G., and Mann, F. C.: *Effect of Experimental Cirrhosis on the Intrahepatic Circulation of Blood in the Intact Animal*, *Arch. Path.* **33**:198 (Feb.) 1942.

in the hepatic sinusoids in rats. If the carbon tetrachloride was removed at once, the circulation returned to its normal state within half a minute. If the inhalation of carbon tetrachloride was continued for thirty minutes, hepatic injury resulted. Maximal toxic effects were evident twenty-four hours later. At that time hepatic enlargement with fatty degeneration, hydropic changes and small hemorrhages were observed. Many of the sinusoids were obliterated from pressure of the swollen hepatic cells, and the liver was anemic in consequence. The sinusoids that remained active were tortuous and irregular in caliber from such pressure. Sinusoids supplied by the hepatic artery were more numerous than those arising from the portal vein. Several weeks after a single inhalation of carbon tetrachloride the livers had regained their normal appearance.

The repeated inhalation of carbon tetrachloride produced cirrhosis of the liver. Wakim and Mann found that in rats the vascular changes consisted of an early initial vasoconstriction during the period of inhalation. This was followed by a prolonged secondary obliteration of the vascular channels, especially venous, in consequence of the swelling and fatty degeneration of the hepatic parenchyma. With advanced cirrhosis there were further collapse and obliteration of the vessels. In the areas of regenerating hepatic parenchyma there was an extreme disorganization in the distribution of the blood vessels. The majority of the sinusoids in such areas were supplied by arterial rather than by venous blood. These studies, therefore, further emphasize the great disorganization of the blood supply in cirrhosis of the liver.

#### PORTAL HYPERTENSION AND THE CRUVEILHIER-BAUMGARTEN SYNDROME

The syndrome of portal hypertension is well recognized.<sup>25</sup> While in the majority of cases the syndrome is associated with hepatic cirrhosis, this is not necessarily so, and the clinical syndrome may be produced by any condition which produces portal hypertension. Such an occurrence is illustrated by a case reported by Reich,<sup>26</sup> in which portal phlebosclerosis was associated with apparently congenital narrowing of the portal vein.

A related type of disturbance is represented in the cases described as instances of the Cruveilhier-Baumgarten syndrome. The 55 cases of this syndrome on record have been reviewed by Armstrong and his

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25. Greene, C. H.; Plotz, M., and Localio, S. A.: Liver and Biliary Tract: A Review for 1937, *Arch. Int. Med.* **61**:655 (April) 1938.

26. Reich, N. E.: Primary Portal Phlebosclerosis, *Arch. Int. Med.* **69**:117 (Jan.) 1942.



associates.<sup>27</sup> They point out that this title may be applied to the condition of patients having the clinical picture of portal hypertension featured by evidence of an excessive umbilical circulation and the presence of a loud abdominal murmur and thrill. The other symptoms, abdominal distention, digestive disturbances, hematemesis and splenomegaly, are to be related to the portal hypertension.

Armstrong and his associates divide these cases into several groups.

1 *A.*—Cases in which the clinical picture is associated with patency of the umbilical vein, atrophy of the liver with little or no cirrhosis and splenomegaly. This group represents a separate category dependent on the presence of a distinct congenital anomaly, namely, a patent umbilical vein. Armstrong and co-workers report these cases, 5 in all, as examples of Cruveilhier-Baumgarten disease. The atrophy of the liver they consider to be associated with hypoplasia of the portal system and reduction in the hepatic circulation.

1 *B.*—Cases in which the umbilical vein is patent but in which there is associated advanced portal cirrhosis. In this group the authors assume that the cirrhosis developed in a patient who coincidentally had a congenitally patent umbilical vein. The portal hypertension developing in consequence of the cirrhosis then led to further dilatation of the umbilical vein.

2 *A.*—Cases of portal hypertension from disease of the liver or portal system with unusually prominent paraumbilical veins. This is the largest group, and the situation is the most probable in cases of cirrhosis with loud venous hum or murmur or marked caput medusae.

2 *B.*—Cases of portal hypertension with patency of other collateral veins in the umbilical area.

This distinction between Cruveilhier-Baumgarten disease and Cruveilhier-Baumgarten syndrome and the reclassification of cases of the latter according to the vessels involved promises to obviate considerable confusion with regard to the recognition of these conditions in the future.

#### LEPTOSPIROSIS ICTEROHAEMORRHAGICA

The literature dealing with leptospirosis icterohaemorrhagica (Weil's disease) was reviewed by Greene and Farrell in 1940.<sup>28</sup> In the past year additional cases were reported from this country by Ashe, Pratt-

27. Armstrong, E. L.; Adams, W. L., Jr.; Tragerman, L. J., and Townsend, E. W.: The Cruveilhier-Baumgarten Syndrome: Review of the Literature and Report of Two Additional Cases, *Ann. Int. Med.* **16**:113 (Jan.) 1942.

28. Greene, C. H., and Farrell, E.: Liver and Biliary Tract: A Review for 1939, *Arch. Int. Med.* **65**:847 (April) 1940.

Thomas and Kumpe,<sup>29</sup> White and Prevost,<sup>30</sup> Rathbun and Waghelstein,<sup>31</sup> Reid and Holt<sup>32</sup> and Stiles and Sawyer.<sup>33</sup> The last-named authors report that they were able to collect a total of 73 authentic cases from North America, with half as many additional cases which had been reported but in which the laboratory proof of leptospirosis was not regarded as adequate. In a footnote they report their knowledge of more than a score of additional and unrecorded cases which were not included in their tabulations. These figures emphasize both the increasing importance of Weil's disease in the United States and the increasing frequency with which this clinical syndrome is being recognized by members of the medical profession.

Ashe and his associates divide the clinical course of the disease into three stages, which are important for diagnosis, though the line of clinical demarcation is not sharp. The onset is abrupt, with severe headaches, muscular pains, backache and high temperature. Marked leukocytosis usually is present. This is the so-called septicemic stage, with leptospiras circulating in the blood stream. They may be recognized in the serum by dark field examination. Stiles and Sawyer, as well as Fennel<sup>34</sup> and Raven,<sup>35</sup> cite an extensive literature, pointing out that confusing artefacts are commonly found on dark field examination of body tissues or fluids and that these pseudospirochetes have been reported in the tissues and fluids of persons in good health and in those of patients suffering from other diseases. The finding of leptospiras in the serum or urine on dark field examination, therefore, should always be confirmed by inoculation of a guinea pig.

The second stage of the disease is associated with the development of jaundice in 40 to 100 per cent of cases. The jaundice appears about the fifth day. At about this time the organisms disappear from the blood and appear in the urine, while specific antibodies appear in the serum.

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29. Ashe, W. F.; Pratt-Thomas, H. R., and Kumpe, C. W.: Weil's Disease: A Complete Review of American Literature and an Abstract of the World Literature; Seven Case Reports, *Medicine* **20**:145 (May) 1941.

30. White, J. J., and Prevost, J. V.: Weil's Disease: Report of Three Cases, Including the Morbid Anatomy of One Case, and a Brief Review of the Pertinent Literature, *Ann. Int. Med.* **15**:207 (Aug.) 1941.

31. Rathbun, H. K., and Waghelstein, J. M.: Weil's Disease: Report of Six Cases, *Ann. Int. Med.* **15**:395 (Sept.) 1941.

32. Reid, J. D., and Holt, R. A.: Spirochetal Jaundice in Virginia with Special Reference to Laboratory Diagnostic Methods, *Virginia M. Monthly* **68**:571 (Oct.) 1941.

33. Stiles, W. W., and Sawyer, W. A.: Leptospiral Infection (Weil's Disease) as an Occupational Hazard, *J. A. M. A.* **118**:34 (Jan. 3) 1942.

34. Fennel, E. A.: Weil's Disease and Artefacts, *Proc. Staff Meet., Clin., Honolulu*, March 1938, vol. 4.

35. Raven, C.: Canine Leptospirosis in Pennsylvania, *J. Infect. Dis.* **69**:131 (Sept.-Oct.) 1941.

The third stage, or convalescence, begins in the latter part of the second week of the disease (fourteen to sixteen days after onset). By then defervescence occurs, and the jaundice begins to clear. A short relapse is not uncommon but usually is not serious. In the third and subsequent weeks of the disease specific agglutinins appear in the serum in high titer. Agglutinations in a dilution of 1 : 300 or over are generally considered as diagnostic. Likewise, a negative reaction after the thirtieth day of illness rules out Weil's disease.

The mortality increases with age. Stiles and Sawyer report a mortality in the American series of 17 per cent for patients under 40 years and of 63 per cent for patients over 40 years of age. The total mortality was 33 per cent. By contrast, the mortality in the Netherlands series was only 11.9 per cent. This difference, however, is probably due not to a difference in the severity of the infection but to the greater number of cases in the European series in which the disease was mild and jaundice was absent.

Stiles and Sawyer point out that if an occupation exposes a worker to contact with rats or dogs or to water or moist material contaminated by the urine of these animals, he is exposed to a risk of leptospiral infection greater than the risk run in private life. They therefore emphasize that under such circumstances Weil's disease is not an occupational disease but rather an occupational hazard. This is sufficiently accepted that Weil's disease is now a compensable disability under the workmen's compensation acts of England, Germany and Australia, as well as that of New York.

#### VITAMIN K AND BLOOD COAGULATION

Scientific interest in the problem of blood coagulation continues unabated. Howell<sup>36</sup> was one of the pioneers in the development of this field, so that it is most appropriate at the present time that he should summarize the recent advances. These are twofold. On the one hand, there is the introduction of heparin into clinical medicine as an anti-coagulant to prevent the formation of thrombi after mechanical or chemical injury to the lining of the heart or blood vessels; on the other hand, there is the use of vitamin K to restore the coagulability of the blood to normal in cases of hypoprothrombinemia. The uses of heparin are not within the scope of this review.

The literature on the clinical and experimental studies on vitamin K has previously been reported in detail.<sup>37</sup> Reference was made then

36. Howell, W. H.: Recent Advances in the Problem of Blood Coagulation Applicable to Medicine, *J. A. M. A.* **117**:1059 (Sept. 27) 1941.

37. (a) Greene, C. H., and Hotz, R.: Liver and Biliary Tract: A Review for 1938, *Arch. Int. Med.* **63**:778 (April) 1939. (b) Greene, C. H.: Liver and Biliary Tract: A Review for 1940, *ibid.* **67**:867 (April) 1941.

to the numerous monographs on vitamin K which had appeared within the past year or so. This list has now been extended in the monographs of Butt and Snell<sup>38</sup> and Koller.<sup>39</sup>

Increased experience in the study of the prothrombin content of the blood in various conditions has led to general agreement that the prothrombin of the blood of newborn infants is decreased temporarily during the first week of life. This hypoprothrombinemia is an important factor in the causation of neonatal cerebral hemorrhage. Hypoprothrombinemia in the newborn can be corrected by injection of synthetic vitamin K<sup>40</sup> or by inunction with an ointment containing the vitamin,<sup>41</sup> but the simplest method is to give synthetic vitamin K to mothers, either orally or by injection during labor.<sup>42</sup> A satisfactory therapeutic response has

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38. Butt, H. R., and Snell, A. M.: Vitamin K, Philadelphia, W. B. Saunders Company, 1941.

39. Koller, F.: Das Vitamin K und seine klinische Bedeutung, Leipzig, Georg Thieme, 1941.

40. Damm, P. N.: Hemorrhagic Diathesis in the New Born, Especially with Regard to Treatment with Blood Transfusion, *Ugesk. f. læger* **102**:620 (June 13) 1940. Fiechter, N.: Hypoprothrombinemia and Hemorrhagic Diathesis of the New Born and Its Relations to Vitamin K, *Monatschr. f. Geburtsh. u. Gynäk.* **111**:1 (Aug.) 1940. Grossman, A. M.: Coagulation Defects in Infancy and Childhood: Frequency of Hypoprothrombinemic States and Their Treatment with Vitamin K; Reclassification of Hemorrhagic Hypoprothrombinemia Neonatorum, *J. Pediat.* **19**:205 (Aug.) 1941. Javert, C. T., and Mann, C.: Prothrombin Concentration in Normal Pregnancy, *Am. J. Obst. & Gynec.* **42**:115 (Sept.) 1941. Maumenee, A. E.; Hellman, L. M., and Shettles, L. B.: Factors Influencing Plasma Prothrombin in New-Born Infants: Effect of Antenatal Administration of Vitamin K on Incidence of Retinal Hemorrhage in New Born, *Bull. Johns Hopkins Hosp.* **68**:158 (Feb.) 1941. Norris, R. F., and Bennett, M. C.: Plasma Prothrombin Values of Mothers and Infants at Delivery: Further Studies Including Comparative Values of Umbilical Arteries and Veins, *Surg., Gynec. & Obst.* **72**:758 (April) 1941. Stevens, R. J.: Vitamin K and Its Use in Prevention and Treatment of Hemorrhage, *West Virginia M. J.* **37**:206 (May) 1941.

41. de Beer, E. J.; Drekar, L., and Flusser, B.: Routes of Administration of Material Capable of Acting as Vitamin K, *Proc. Soc. Exper. Biol. & Med.* **46**:535 (April) 1941. Russell, H. K., and Page, R. C.: Effect of Topical Application of 2-Methyl-1,4-Naphthoquinone (Synthetic Vitamin K Analogue) on Prothrombin Level of New Born Infants, with Reference to Simplified Microprothrombin Test, *Am. J. M. Sc.* **202**:355 (Sept.) 1941.

42. Astrowe, P. S.; Palmerton, E. S., and Henderson, V.: Clinical Studies with Vitamin K in New-Born Infants, *J. Pediat.* **18**:507 (April) 1941. Huber, C. P., and Shrader, J. S.: Blood Prothrombin Levels in New Born, *Am. J. Obst. & Gynec.* **41**:566 (April) 1941. Mull, J. W.; Bill, A. H., and Skowronska, H.: Effect on New Born of Vitamin K Administered to Mothers in Labor, *J. Lab. & Clin. Med.* **26**:1305 (May) 1941. Valentine, E. H.; Reinhold, J. G., and Schneider, E.: Effectiveness of Prenatal Administration of 2-Methyl-1,4-Naphthoquinone in Maintaining Normal Prothrombin Levels in Infants, *Am. J. M. Sc.* **202**:359 (Sept.) 1941.

been obtained in infants after intravenous injection in mothers only ten minutes before delivery.<sup>43</sup> The administration of vitamin K to women at term, therefore, is rapidly becoming a routine procedure for the protection of infants and for the prevention of neonatal hemorrhage.

Reports of clinical experience continue to be uniformly enthusiastic regarding the value of vitamin K in the treatment of cholemic bleeding and the other manifestations of a deficiency of prothrombin associated with jaundice and hepatic disease.<sup>44</sup>

Observers are in agreement that in a small proportion of cases there is no response to treatment with vitamin K, even though the latter is administered intravenously or intramuscularly. In such cases evidence of marked hepatic damage has been found.<sup>45</sup> The failure of a patient

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43. Bohlender, G. P.; Rosenbaum, W. M., and Sage, E. C.: Antepartum Use of Vitamin K in the Prevention of Prothrombin Deficiency in the New Born, *J. A. M. A.* **16**:1763 (April 19) 1941.

44. Quick, A. J.: Therapeutic Value and Limitation of Vitamin K, *Nebraska M. J.* **26**:1 (Jan.) 1941. Anderson, E. R.; Karabin, J. E.; Udesky, H. L., and Seed, L.: Oral Administration of Synthetic Vitamin K (2-Methyl-1,4-Naphthoquinone), *Surgery* **9**:361 (March) 1941. Zenker, R., and Meurer, H.: Vitamin K in Surgery, *München. med. Wchnschr.* **88**:622 (May 30) 1941. Collier, F. A., and Farris, J. M.: Management of Jaundiced Patient with Special Reference to Vitamin K, *Surg., Gynec. & Obst.* **73**:21 (July) 1941. Tourinho, R.: Vitamin K in Surgery, *Hospital, Rio de Janeiro* **19**:755 (May) 1941.

45. Warner, E. D.: Plasma Prothrombin: Effect of Partial Hepatectomy, *J. Exper. Med.* **68**:831, 1938. Bollman, J. L.; Butt, H. R., and Snell, A. M.: The Influence of the Liver on the Utilization of Vitamin K, *J. A. M. A.* **115**:1087 (Sept. 28) 1940. Brinkhous, K. M., and Warner, E. D.: Effect of Vitamin K on Hypoprothrombinemia of Experimental Liver Injury, *Proc. Soc. Exper. Biol. & Med.* **44**:609 (June) 1940. Andrus, W. D.; Lord, J. W., Jr., and Moore, R. A.: The Effect of Hepatectomy on the Plasma, Prothrombin and the Utilization of Vitamin K, *Surgery* **6**:899 (Dec.) 1939. Lord, J. W., Jr.; Andrus, W. D., and Moore, R. A.: Metabolism of Vitamin K and Role of the Liver in Production of Prothrombin in Animals, *Arch. Surg.* **41**:585 (Sept.) 1940. Rhoads, J. E.: Physiological Factors Regulating the Level of the Plasma Prothrombin, *Ann. Surg.* **111**:916 (May) 1940. Allen, J. G., and Julian, O. C.: Clinical Use of a Synthetic Substance Resembling Vitamin K (2-Methyl-1,4-Naphthoquinone), *Arch. Surg.* **40**:912 (May) 1940. Butt, H. R.; Snell, A. M.; Osterberg, A. E., and Bollman, J. L.: Treatment of Hypoprothrombinemia: Use of Various Synthetic Compounds Exhibiting Antihemorrhagic Activity (Vitamin K<sub>1</sub> Activity), *Proc. Staff Meet., Mayo Clin.* **15**:69 (Jan. 31) 1940. Scanlon, G. H.; Brinkhous, K. M.; Warner, E. D.; Smith, H., and Flynn, J. E.: Plasma Prothrombin and the Bleeding Tendency with Special Reference to Jaundiced Patients and Vitamin K Therapy, *J. A. M. A.* **112**:1898 (May 13) 1939. Butt, H. R., and Leary, W. V.: Diseases of Nutrition, *Arch. Int. Med.* **67**:411 (Feb.) 1941. Andrus, W. DeW.: The Newer Knowledge of Vitamin K, *Bull. New York Acad. Med.* **17**:116 (Feb.) 1941. Reid, J.: Prothrombin Deficiency in Disease of the Liver and Bile Passages and Its Treatment with Synthetic Vitamin K, *Brit. M. J.* **1**:579 (April) 1941. Lord, J. W., Jr., and Andrus, W. D.: Differentiation of Intrahepatic and Extra-

to respond to intensive therapy with vitamin K not only is of value in differential diagnosis but is of serious prognostic import. Because in some instances there seems to be confusion on this point, it should be emphasized that a prolonged prothrombin time in an untreated patient usually is an accompaniment of the jaundice and a consequence of the interference with the flow of bile into the intestine. It therefore is evidence of a deficiency of vitamin K and not a measure of hepatic injury. It is the failure of such a patient to respond to adequate and preferably parenteral therapy that indicates functional incapacity of the liver.

Soon after the isolation of the naturally occurring vitamin K<sub>1</sub> it was shown to have the chemical structure of 2-methyl-3-phytyl-1,4-naphthoquinone. This led to the testing of related chemical compounds, and menadione (2-methyl-1,4-naphthoquinone) was found to be one of the most active. Because of its activity and the ease with which it is prepared synthetically, it has largely replaced the natural vitamin K<sub>1</sub> in therapy. Menadione, while readily soluble in oil, has been considered too insoluble in water for intravenous or intramuscular injection. Water-soluble compounds possessing prothrombogenic properties have been sought, and several such compounds have been described and introduced into clinical medicine. Four-amino-2-methyl-1-naphthol hydrochloride, marketed by Parke, Davis & Company as synkamin;<sup>46</sup> 2-methyl-1,4-naphthohydroquinone diphosphoric acid ester tetra sodium salt, marketed by Hoffmann-Laroche Inc. as synkayvite,<sup>47</sup> and 2-methyl-1,4-naphthohydroquinone-3-sodium sulfonate, marketed by the Abbott Laboratories,<sup>48</sup> have been reported to be of clinical value.

It may be accepted that all these preparations are effective in the treatment of hypoprothrombinemia. When given by mouth they are

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hepatic Jaundice: Response of Plasma Prothrombin to Intramuscular Injection of Menadione (2-Methyl-1,4-Naphthoquinone) as a Diagnostic Aid, *Arch. Int. Med.* **68**:199 (Aug.) 1941. Stewart, J. D.: Clinical Significance of Prothrombin Deficiency and Its Treatment, *Ann. Surg.* **114**:907 (Nov.) 1941. Tocantins, L. M., and Jones, H. W.: Hypoprothrombinemia: Effect of Peroral and Parenteral Administration of Synthetic Vitamin K Substitute (2-Methyl-1,4-Naphthoquinone), *ibid.* **113**:276 (Feb.) 1941. Ziffren, S. E.; Owen, C. A.; Warner, E. D., and Peterson, T. R.: Hypoprothrombinemia and Liver Function, *Surg., Gynec & Obst.* **74**:463 (Feb., no. 2A) 1942.

46. Sharp, E. A.; von der Heide, E. G., and Good, W. H.: Vitamin K Activity of 2-Methyl-1,4-Naphthoquinone and 4-Amino-2-Methyl-1-Naphthol in Hypoprothrombinemia, *J. Lab. & Clin. Med.* **26**:818 (Feb.) 1941.

47. Lee, J.; Solmssen, U. V.; Steyermark, A., and Foster, R. H. K.: Antihemorrhagic Activity of Tetra Sodium 2-Methyl-1,4-Naphthohydroquinone Diphosphoric Acid Ester and Other Naphthoquinone Derivatives, *Proc. Soc. Exper. Biol. & Med.* **45**:407 (Oct.) 1940. Almquist, H. J., and Klose, A. A.: Comparative Activities of Certain Antihemorrhagic Compounds, *ibid.* **45**:55 (Oct.) 1940.

48. Davison, M.; Steigmann, F., and Udesky, H. L.: Clinical Studies on the Antihemorrhagic Effects of a New Water-Soluble Vitamin K-Like Substance, *Surg., Gynec. & Obst.* **74**:35 (Jan.) 1942.

readily absorbed without the simultaneous administration of bile salts. They may be given subcutaneously or intravenously when parenteral therapy is indicated. Olwin<sup>49</sup> reports that a satisfactory therapeutic response was obtainable with each of these preparations. He found in addition that menadione was sufficiently soluble in distilled water to permit the preparation of a 0.01 per cent solution. He gave this solution intravenously in doses of 0.1 to 12 mg., with satisfactory therapeutic responses. To date, there would seem to be little evidence to indicate a basis for choice between these different compounds.

#### EFFECT OF DIET ON THE LIVER

Not only does the character of the diet determine the work performed by the liver in the metabolism and oxidation of the food, but it may have an effect on the ability of the liver to carry out that work. Greene and Farrell,<sup>28</sup> Madden and Whipple,<sup>50</sup> Hawkins<sup>51</sup> and Mann<sup>52</sup> have summarized the recent literature on the role of the liver in protein metabolism and in the production and utilization of the plasma proteins. The importance of an adequate supply of protein in the diet to maintain reserves of protein in the liver and to increase its resistance to injury by various toxic agents has been emphasized.

Most investigators are in agreement that an undue increase in the amount of fat present in the liver contributes to the development of cirrhosis. The relation of the liver to fat metabolism has been reviewed recently by Greene, Handelsman and Babey,<sup>1</sup> Best and Ridout<sup>53</sup> and Channon.<sup>54</sup> Many different factors acting either singly or in combination may produce an increase in the amount of fat in the liver. Feeding a high fat diet will produce a permanent increase, which contrasts with the temporary increase produced by fasting. Overfeeding even of a high carbohydrate diet may produce a fatty liver in consequence of the production of fat from carbohydrate. This is particularly true in birds, such as geese.<sup>55</sup> Thiamine, or vitamin B<sub>1</sub>, will increase the

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49. Olwin, J. H.: The Intravenous Use of Vitamin K, *J. A. M. A.* **117**:432 (Aug. 9) 1941.

50. Madden, S. C., and Whipple, G. H.: Plasma Proteins: Their Source, Production and Utilization, *Physiol. Rev.* **20**:194 (April) 1940.

51. Hawkins, W. B.: Liver and Bile, in Luck, J. M., and Hall, V. E.: Annual Review of Physiology, Stanford University, Calif., Annual Reviews, Inc., 1941, vol. 3, p. 259.

52. Mann, F. C.: The Liver and Medical Progress, *J. A. M. A.* **117**:1577 (Nov. 8) 1941.

53. Best, C. H., and Ridout, J. H.: Choline as a Dietary Factor, in Luck, J. M., and Smith, J. H. C.: Annual Review of Biochemistry, Stanford University, Calif., Annual Reviews, Inc., 1939, vol. 8, p. 439.

54. Channon, J. H.: Fat Metabolism, in Luck, J. M., and Smith, J. H. C.: Annual Review of Biochemistry, Stanford University, Calif., 1940, vol. 9, p. 231.

55. Flock, E. V.; Bollman, J. L.; Hester, H. R., and Mann, F. C.: Fatty Liver in the Goose Produced by Overfeeding, *J. Biol. Chem.* **121**:117 (Oct.) 1937.

amount of fat in the liver under certain experimental conditions by stimulating the formation of fat from carbohydrate.<sup>56</sup> Pyridoxine, or vitamin B<sub>6</sub>, and biotin, or vitamin H, have been implicated in increasing the fat in the liver. The chronic fatty infiltration of the liver reported in pancreatectomized dogs and some patients with diabetes is well recognized. The use of extracts of anterior pituitary will produce a fatty liver.<sup>57</sup> Diethylstilbestrol and some other estrogens have been reported to produce fatty livers, though this is denied by other investigators.<sup>58</sup> The concentration of cholesterol in the liver tends to vary with the neutral fat, though it is deposited to a lesser degree, but if cholesterol is fed then it may become the predominant lipid in the liver.<sup>59</sup>

An increase in the amount of protein or carbohydrate in the diet usually decreases the amount of fat in the liver. Choline<sup>60</sup> or pancreatic extract<sup>61</sup> will prevent the accumulation of fat due to a high fat diet. Lipocaic has been described as the fat-metabolizing hormone of the pancreas, but its physiologic status is still undecided.<sup>62</sup>

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56. McHenry, E. W., and Gavin, G.: The Effect of Several B Vitamins and of Choline upon Liver and Body Fat, *J. Biol. Chem.* **128**:66 (June) 1939; The B Vitamins and Fat Metabolism: IV. The Synthesis of Fat from Protein, *ibid.* **138**:471 (April) 1941; The Effect of Biotin upon the Synthesis of Lipids in Rats, *ibid.* **140**:lxxxvii (July) 1941.

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62. Dragstedt, L. R.; Van Prohaska, J., and Harms, H. P.: Observations on a Substance in Pancreas (a Fat Metabolizing Hormone) Which Permits Survival



That prolonged fatty infiltration of the liver is harmful and may be one of the factors responsible for the development of cirrhosis is accepted. Much of the literature was reviewed by Connor<sup>63</sup> in his study of the relation of fatty livers to alcoholism and their role in the development of alcoholic cirrhosis. This topic was reviewed by Greene and Hotz.<sup>37a</sup>

Chloroform and carbon tetrachloride have been the favored poisons for the experimental production of injury to the liver. Other poisons, however, are being used. McCulloch<sup>64</sup> reports that the admixture of seeds of the yellow tarweed *Amsinckia intermedia* with the feed will produce cirrhosis of the liver in domestic animals. It has not yet been tried in the smaller laboratory animals.

Foodstuffs grown on soils rich in selenium have been found to be toxic. This has been shown to be due to the passage of selenium from the soil into forage or grains raised on it. The symptoms and pathologic changes found in experimental animals with chronic selenium poisoning are various, but atrophic nodular cirrhosis of the liver is reported in cases of more severe poisoning.<sup>65</sup> The experimental studies of Smith and associates<sup>66</sup> and Lewis, Schultz and Gortner<sup>67</sup> have shown that

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and Prevents Liver Changes in Depancreatized Dogs, *Am. J. Physiol.* **117**:175-181 (Sept.) 1936. Dragstedt, L. R.: Present Status of Lipocaic, *J. A. M. A.* **114**:29 (Jan. 6) 1940. Vermeulen, C.; Dragstedt, L. R.; Clark, D. E.; Julian, O. C., and Allen, J. G.: Effect of the Administration of Lipocaic and Cholesterol in Rabbits, *Arch. Surg.* **44**:260-267 (Feb.) 1942. Gavin, G., and McHenry, E. W.: B. Vitamins and Fat Metabolism Synthesis of Fat from Protein, *J. Biol. Chem.* **141**:619 (Nov.) 1941. Isabolinskaya, R. M.: The Lipocaic of the Pancreas and the Fat-Carbohydrate Metabolism, *Bull. biol. et méd. expér. URSS* **9**:107, 1940.

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64. McCulloch, E. C.: The Experimental Production of Hepatic Cirrhosis by the Seed of *Amsinckia intermedia*, *Science* **91**:95 (Jan. 26) 1940.

65. Smith, M. I., and Westfall, B. B.: Further Field Studies on the Selenium Problem in Relation to Public Health, *Pub. Health Rep.* **52**:1375 (Oct. 1) 1937.

66. Smith, M. I.: The Influence of Diet on the Chronic Toxicity of Selenium, *Pub. Health Rep.* **54**:1441 (Aug. 4) 1939. Lillie, R. D., and Smith, M. I.: Histogenesis of Hepatic Cirrhosis in Chronic Food Selenosis, *Am. J. Path.* **16**:223 (March) 1940. Smith, M. I., and Stohlgman, E. F.: Further Observations on Influence of Dietary Protein on Toxicity of Selenium, *J. Pharmacol. & Exper. Therap.* **70**:270 (Nov.) 1940. Smith, M. I.: Chronic Endemic Selenium Poisoning: A Review of the More Recent Field and Experimental Studies, *J. A. M. A.* **116**:562 (Feb. 15) 1941.

67. Lewis, H. B.; Schultz, J., and Gortner, R. A., Jr.: Dietary Protein and Toxicity of Sodium Selenite in White Rats, *J. Pharmacol. & Exper. Therap.* **68**:292 (Feb.) 1940. Gortner, R. A., Jr.: Chronic Selenium Poisoning of Rats as Influenced by Dietary Protein, *J. Nutrition* **19**:105 (Feb.) 1940.

selenium was most toxic when the experimental animals were fed a low protein, high carbohydrate diet. The toxic symptoms were much less marked when a high protein diet was fed. A high fat diet was not as harmful as was the low protein diet.

Arsenic has an 'injurious effect on the liver. Messinger and Hawkins<sup>68</sup> report that a high protein diet would protect dogs against toxic doses of arsphenamine. Carbohydrate was less beneficial, while a high fat diet was harmful. Von Glahn, Flinn and Keim<sup>69</sup> fed sodium arsenate to rabbits on a diet of hay and oats and were able to produce hepatic necrosis and mild degrees of cirrhosis. Carbohydrates in the form of white bread and potatoes reduced the degree of hepatic injury. Brewers' yeast also reduced the severity of the damage and prolonged the life of the experimental animals.

Evidence is being accumulated that dietary factors other than the relative amounts of carbohydrate, protein and fat in the diet affect the liver. György and Goldblatt<sup>70</sup> observed that when young rats were kept on a diet devoid of vitamin B but supplemented with thiamine, riboflavin and pyridoxine they showed evidence of hepatic injury. This consisted primarily of acute diffuse necrosis with fatty infiltration. In some instances considerable periportal fibrosis was observed. Rats fed on the same basal diet supplemented with yeast or yeast extract did not show any pathologic changes in the liver. Shortly afterward, Rich and Hamilton<sup>71</sup> reported the development of cirrhosis of the liver on a nutritional basis in rats, while Spellberg, Keeton and Ginsberg<sup>72</sup> made similar observations in guinea pigs. In both studies the addition of

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68. Messinger, W. J., and Hawkins, W. B.: Arsphenamine Liver Injury Modified by Diet Protein and Carbohydrate Protective but Fat Injurious, *Am. J. M. Sc.* **199**:216 (Feb.) 1940.

69. von Glahn, W. C.; Flinn, F. B., and Keim, W. F., Jr.: Effect of Certain Arsenates on the Liver, *Arch. Path.* **25**:488 (April) 1938. von Glahn, W. C., and Flinn, F. B.: The Effect of Yeast on the Incidence of Cirrhosis Produced by Lead Arsenate, *Am. J. Path.* **15**:771 (Nov.) 1939.

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yeast to the diet prevented the development of the changes in the liver. The earlier studies of Curtis and Newburgh and others<sup>73</sup> had shown that an excess of cystine in the diet would produce acute hepatic necrosis. Studies by György, Poling and Goldblatt<sup>74</sup> and Blumberg and McCollum<sup>75</sup> showed that the addition of extra cystine to the experimental diet of rats accentuated the development of cirrhosis. Yeast or choline prevented the cirrhosis even though extra cystine was fed. Similar results are reported by Lillie, Daft and Sebrell,<sup>76</sup> who produced cirrhosis in rats by the use of a diet low in protein and fat with added cystine. The cirrhosis was prevented by feeding choline, methionine or casein, either singly or in combination. Supplying 20 per cent alcohol to the rats in place of drinking water apparently had no influence on the results.

The clinical counterpart of some of these experimental studies is presented by Patek and Post.<sup>77</sup> They emphasize the frequency in cases of portal cirrhosis of alcoholism, a deficient diet, loss of weight, malnutrition and a specific deficiency of the vitamin B complex. This latter was shown by the frequency of polyneuritis, "pellagrous" dermatitis and atrophy of the lingual papillae. A group of 54 patients with portal cirrhosis therefore were placed on a highly nutritious diet together with vitamin B complex. This diet contained 149 Gm. of protein, 175 Gm. of fat and 365 Gm. of carbohydrate. This was supplemented by the

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77. Patek, A. J., Jr.: Treatment of Alcoholic Cirrhosis of the Liver with High Vitamin Therapy, *Proc. Soc. Exper. Biol. & Med.* **37**:329 (Nov.) 1937. Patek, A. J., Jr., and Post, J.: Treatment of Cirrhosis of the Liver by a Nutritious Diet and Supplements Rich in Vitamin B Complex, *J. Clin. Investigation* **20**:481 (Sept.) 1941.

addition of 50 Gm. of brewers' yeast and 5 mg. of thiamine hydrochloride daily. Twice weekly 5 cc. of concentrated liver extract (15 U. S. P. units per cubic centimeter) was given intramuscularly. The control series was obtained by a study of the records of 386 patients with cirrhosis treated in various metropolitan hospitals. The initial course of the disease before the institution of treatment was similar in the two groups of patients.

The response of the patients treated by Patek and Post was much more satisfactory than was that of the control series. After the onset of ascites 72 per cent of the treated patients were alive for more than six months, while only 57 per cent of the control patients survived for this period. At the end of the second year, 45 per cent of the treated patients were alive as compared to 21 per cent of the control series. In addition to an increased period of survival, there were signs of general physical improvement. In a significant number of cases the disappearance of ascites, edema, jaundice or vascular spiders was noted. The level of the serum albumin and globulin returned toward normal, while the Takata-Ara, the cephalin flocculation and the bromsulphalein tests showed improvement.<sup>78</sup>

Closely related to the studies of the production of cirrhotic changes in the liver by dietary means are the studies of the effects of diet on the production of experimental cancer of the liver. The demonstration that cancer of the skin could be produced by the persistent application of gas works tar<sup>79</sup> led to a hunt for carcinogenic substances. It is now known that many chemical compounds have carcinogenic properties.<sup>80</sup> One of these is the dye N-N dimethylaminoazobenzene (butter yellow). If the dye is fed to rats on a diet of unpolished rice and carrots, a primary cancer of the liver is produced.<sup>81</sup> Adding dried liver, yeast or riboflavin and casein to this regimen prevents the development of the cancer. Methionine, cystine and choline likewise have a protective

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78. Patek, A. J., Jr.; Post, J., and Victor, J. C.: The Vascular "Spider" Associated with Cirrhosis of the Liver, *Am. J. M. Sc.* **200**:341 (Sept.) 1940. Hanger, F. M., and Patek, A. J., Jr.: The Cephalin Flocculation Test in Cirrhosis of the Liver, *ibid.* **202**:48 (July) 1941. Post, J., and Patek, A. J., Jr.: Serum Proteins in Cirrhosis of the Liver: I. Relation to Prognosis and to Formation of Ascites, *Arch. Int. Med.* **69**:67 (Jan.) 1942; II. Nitrogen Balance Studies on Five Patients, *ibid.* **69**:83 (Jan.) 1942.

79. Yamagiwa, K., and Ichikawa, K.: Experimentelle Studien über die Pathogenese der Epithelialgeschwulste, *Mitt. a. d. med. Fak. d. k. Univ. zu Tokyo* **15**:295, 1916.

80. Kinoshita, R.: The Changes in the Liver of the Rat Caused by 4-Dimethylaminobenzene-1-Azo-1-Naphthalene, and Related Compounds, *Gann* **34**:164-167 (June) 1940.

81. Kinoshita, R.: Studies on the Cancerogenic Azo and Related Compounds, *Yale J. Biol. & Med.* **12**:287 (Jan.) 1940.

effect.<sup>82</sup> On the other hand, the recent experiments of du Vigneaud and his associates<sup>83</sup> and of György, Landy and Goldblatt<sup>84</sup> are of especial interest in showing that biotin (vitamin H) increases the carcinogenic action of the butter yellow.

The first changes in the liver of a rat on this carcinogenic regimen are necrosis and fibrosis suggestive of cirrhosis. The characteristic hepatoma develops later. The similarity between many of the diets used in the experimental production of carcinoma and those used in the production of experimental cirrhosis is of great interest. The clinical experience that hepatoma or primary cancer of the liver develops most commonly on the basis of a preexisting cirrhosis is intriguing.

Rhoads<sup>85</sup> has attempted to study the chemical processes in the cells of the normal liver and the changes in the presence of cancer. Particular attention was paid to the various kinetic enzyme systems with which the different vitamins are associated. These studies indicated that when the rats were on a diet deficient in riboflavin, the administration of butter yellow stimulated the excretion of reserve riboflavin in the urine and so increased the severity of the deficiency. Studies of coenzyme I, a diphosphopyridine nucleotide, which contains nicotinic acid as an essential constituent, showed that the livers of rats on a carcinogenic diet contained normal amounts of coenzyme I. If butter yellow was added to the diet, there was a prompt and serious decrease in the amount of coenzyme I. Tumor tissue contained even smaller amounts of

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82. Ando, T.: Experimentelle Leberkarzinomentstehung und Getreide, *Gann* **32**:252 (June) 1938. Nakahara, W.; Mori, K., and Fujiwara, T.: Inhibiting Effect of Yeast Feeding on Experimental Production of Liver Cancer (Preliminary Note), *ibid.* **32**:465 (Dec.) 1938; Does Vitamin B<sub>1</sub> Inhibit Experimental Production of Liver Cancer? Second Preliminary Note on Effect of Diet on Experimental Production of Liver Cancer, *ibid.* **33**:13 (Feb.) 1939; Inhibiting Effect of Yeast Feeding on Experimental Production of Liver Cancer, *ibid.* **33**:57 (April) 1939; Inhibition of Experimental Production of Liver Cancer by Liver Feeding—Study in Nutrition, *ibid.* **33**:406 (Oct.) 1939. Morigami, S., and Kasiwabara, N.: Inhibition of the Experimental Production of Liver Cancer by Millet Feeding, *ibid.* **35**:65 (April) 1941. Sugiura, K., and Rhoads, C. P.: Experimental Liver Cancer in Rats and Its Inhibition by Rice-Bran Extract, Yeast and Yeast Extract, *Cancer Research* **1**:3 (Jan.) 1941. Kensler, C. J.; Sugiura, K.; Young, N. F.; Halter, C. R., and Rhoads, C. P.: Partial Protection of Rats by Riboflavin with Casein Against Liver Cancer Caused by Dimethylaminoazobenzene, *Science* **93**:308 (March 28) 1941.

83. du Vigneaud, V.; Spangler, J. M.; Burk, D.; Kensler, C. J.; Sugiura, K., and Rhoads, C. P.: The Procarcinogenic Effect of Biotin in Butter Yellow Tumor Formation, *Science* **95**:174 (Feb. 13) 1942.

84. György, P.; Landy, and Goldblatt, H., cited by du Vigneaud and others.<sup>83</sup>

85. Rhoads, C. P.: Recent Studies in the Production of Cancer by Chemical Compounds: The Conditioned Deficiency as a Mechanism, *Bull. New York Acad. Med.* **18**:53 (Jan.) 1942.

coenzyme I than the damaged hepatic cells. Rhoads therefore argues that these observations constitute evidence that the administration of one carcinogenic chemical injures normal hepatic cells by interfering with enzyme systems which are essential for normal chemical function and so for normal life of the cells. Further discussion at the present time is speculative, but these studies promise to open the way for a better understanding of cell function, especially in the liver.

#### THE LIVER AND VITAMIN A

Reference was made a year ago to the accumulating evidence which indicates that there is some deficiency of vitamin A in patients with hepatic disease. Most of these reports, such as the recent studies of Wohl and Feldman and others,<sup>86</sup> are limited to the demonstration of an abnormal visual adaptation to darkness. Such a method, while accepted as satisfactory for the clinical recognition of deficiency of vitamin A, is not applicable to experimental animals.

The introduction of chemical methods of assay for vitamin A has permitted the study of the storage of the vitamin in various organs. The earlier studies of Baumann, Riising and Steenbock and others<sup>87</sup> indicated that the predominant proportion of any surplus intake over the basal requirement is stored in the liver. These studies have been confirmed by Kao and Sherman.<sup>88</sup> Drummond and his associates<sup>89</sup> found the administered vitamin A was uniformly distributed through

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86. Wohl, M. G., and Feldman, J. B.: The Occurrence of Avitaminosis A in Diseases of the Liver, *Am. J. Digest. Dis.* **8**:464 (Dec.) 1941. Jeans, P. C.; Blanchard, E. L., and Satterthwaite, F. E.: Dark Adaptation and Vitamin A: Further Studies with the Biophotometer, *J. Pediat.* **18**:170 (Feb.) 1941. Eckhardt, R. E., and Johnson, L. V.: A Comparison of Two Methods of Measuring Dark Adaptations, *ibid.* **18**:195 (Feb.) 1941. Bajardi, G., and Galeone, A.: La cecità notturna quale sintomo di malattia epatica, *Policlinico (sez. prat.)* **48**:193 (Feb. 3) 1941.

87. Baumann, C. A.; Riising, B. M., and Steenbock, H.: Fat-Soluble Vitamins: The Absorption and Storage of Vitamin A in the Rat, *J. Biol. Chem.* **107**:705 (Dec.) 1934. Moore, T.: Vitamin A and Carotene: The Distribution of Vitamin A and Carotene in the Body of the Rat, *Biochem. J.* **25**:275, 1931. McCoord, A. B., and Luce-Clausen, E. M.: Storage of Vitamin A in Liver of Rat, *J. Nutrition* **7**:557 (May) 1934. Chevallier, A., and Choron, Y.: Sur la teneur du foie en vitamine A et ses variations, *Compt. rend. Soc. de biol.* **120**:1223, 1935.

88. Kao, H. C., and Sherman, H. C.: Influence of Nutritional Intake upon Concentration of Vitamin A in Body Tissues, *Proc. Soc. Exper. Biol. & Med.* **45**:589 (Nov.) 1940.

89. Drummond, J. C.; Gilding, H. P., and Macwalter, R. J.: Fate of Carotene Introduced into Circulation, *J. Physiol.* **82**:75 (Aug. 24) 1934. Drummond, J. C., and Macwalter, R. J.: Fate of Carotene Injected into Circulation of Rat, *ibid.* **83**:236 (Dec. 31) 1935.

the liver. Schneider and Widmann<sup>90</sup> found that the thyrotropic hormone caused a discharge of vitamin A from the liver. Young and Wald<sup>91</sup> found further that the removal of one lobe of the liver brought about a loss of the vitamin from the remaining lobes. This loss was accompanied by an increase of the vitamin in the blood. Stimulation of the splanchnic nerves increased the level of the vitamin in the blood, but stimulation of the middle cervical sympathetic ganglion was without effect. Young and Waldo concluded, therefore, that not only is the liver a storehouse of vitamin A but the vitamin may be mobilized in a manner similar to that in which sugar is mobilized by the liver.

The correlation between the concentration of vitamin A in the blood and the stores in the liver was emphasized by Lewis and his associates<sup>92</sup> and by Horton, Murrill and Curtis<sup>93</sup> on the basis of feeding experiments in rats.

Confirmatory clinical data are provided by several investigators,<sup>94</sup> including Cox and Ralli and her associates, who found much less vitamin A in the livers of patients with cirrhosis than they did in the livers of normal subjects. Not only was the concentration of vitamin A in the plasma reduced in the presence of cirrhosis, but when vitamin A was administered orally in the form of cod liver oil concentrates, the resultant rise in the blood level was much less in patients with cirrhosis than it was in normal subjects.<sup>95</sup>

That a reduction in the concentration of vitamin A in the plasma is not necessarily indicative of cirrhosis or hepatic injury was found

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90. Schneider, E., and Widmann, E.: Ueber Beziehungen des Vitamin A und seiner Vorstufen zur Leberschädigung und zur Widerstandskraft gegenüber Infektionen: VII. Mitteilung der fortgesetzten Untersuchungen über die Hyperthyreosen, *Klin. Wchnschr.* **13**:1497 (Oct. 20) 1934.

91. Young, G., and Wald, G.: Mobilization of Vitamin A by Sympathico-Adrenal System, *Am. J. Physiol.* **131**:210 (Nov.) 1940.

92. Lewis, J. M.; Bodansky, O.; Falk, K. G., and McGuire, G.: Relationship on Vitamin A Blood Level in the Rat to Vitamin A Intake and to Liver Storage, *Proc. Soc. Exper. Biol. & Med.* **46**:248 (Feb.) 1941.

93. Horton, P. B.; Murrill, W. A., and Curtis, A. C.: Vitamin A and Carotene: I. The Determination of Vitamin A in the Blood and Liver as an Index of Vitamin A Nutrition of the Rat, *J. Clin. Investigation* **20**:387 (July) 1941.

94. Breusch, F., and Scalabrino, R.: Die quantitativen Verhältnisse der Leberlipide, *Ztschr. f. d. ges. exper. Med.* **94**:569, 1934. Moore, T.: The Vitamin Reserve of the Adult Human Being in Health and Disease, *Biochem. J.* **31**:155, 1937. Cox, A. J.: Vitamin A Storage in Active and Arrested Cirrhosis, *Am. J. Path.* **15**:647 (Sept.) 1939. Ralli, E. P.; Papper, E.; Paley, K., and Bauman, E.: The Vitamin A and Carotene Content of Normal and Pathological Human Livers, *Arch. Int. Med.* **68**:102 (July) 1941.

95. Lasch, F.: Ueber den Vitamin A-Spiegel im Blute bei Leberkrankheiten, *Klin. Wchnschr.* **17**:1107 (Aug. 6) 1938. Ralli, E. P.; Bauman, E., and Roberts, L. B.: The Plasma Levels of Vitamin A After the Ingestion of Standard Doses: Studies in Normal Subjects and Patients with Cirrhosis of the Liver, *J. Clin. Investigation* **20**:709 (Nov.) 1941.

by Rhoads and his associates.<sup>96</sup> They report that 85 per cent of patients with cancer of the gastrointestinal tract had abnormally low levels of vitamin A in the plasma. Normal concentrations were found in the liver. Cox<sup>97</sup> reports 3 cases of massive necrosis of the liver in which it was possible to compare the concentration of vitamin A in normal and in damaged areas of the same liver. The quantity of vitamin was greater in areas of healing necrosis in which the hepatic cells had been destroyed. Cox, therefore, is in agreement with Lasch and Roller<sup>98</sup> in assuming that the greater part of the storage of vitamin A in the liver is in the Kupffer cells. In the cases reported by Cox, the Kupffer cells had been spared by the agent responsible for the necrosis of the parenchymal cells of the liver.

When frozen sections of tissues are examined with ultraviolet rays, they show a striking green fluorescence, which gradually fades. Popper and Greenberg<sup>99</sup> have demonstrated that this characteristic fluorescence is due to vitamin A. They have been able by this means to visualize the course of vitamin A metabolism in the tissues. The characteristic fluorescence was found in the epithelial and Kupffer cells of the liver, the fascicular layer of the adrenal, the interstitium of the kidney and the lung, the interstitial cell cords and the corpora lutea of the ovary, the pleura, the pericardium, the peritoneum, the meninges, the retina and the pigmented layer of the eye, fat cells and, after ingestion of vitamin A, in the upper part of the small intestine. The amount of fluorescent material in the tissues was reduced by removing vitamin A from the diet and increased by feeding an excess of the vitamin.

The livers of animals deficient in the vitamin showed none of the characteristic fluorescence. In the livers of normal animals the parenchymal cells showed fluorescence in small lipid droplets along the edge of the cytoplasm marking the boundary between the liver cells and the sinusoids. The cytoplasm also had a dimmer fluorescence, indicating a diffuse distribution of minute amounts of vitamin A. The Kupffer cells contained small lipid droplets rich in vitamin A. After ingestion

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96. Abels, J. C.; Gerham, A. T.; Pack, G. T., and Rhoads, C. P.: Metabolic Studies in Patients with Gastro-Intestinal Cancer: III. The Hepatic Concentrations of Vitamin A, *Proc. Soc. Exper. Biol. & Med.* **48**:488 (Nov.) 1941.

97. Cox, A. J.: Site of Vitamin A Storage in the Liver, *Proc. Soc. Exper. Biol. & Med.* **47**:333 (June) 1941.

98. Lasch, F.: Vitamin A-Stoffwechsel und Leber bei Experimenteller Phosphorvergiftung, *Klin. Wchnschr.* **14**:1070 (July 27) 1935. Lasch, F., and Roller, D.: Ueber die Beeinflussung des Vitamin A-Stoffwechsels der Leber durch Blockade des Reticuloendothels, *ibid.* **15**:1636 (Nov. 7) 1936.

99. Popper, H.: Histological Demonstration of Vitamin A in Rats by Means of Fluorescence Microscopy, *Proc. Soc. Exper. Biol. & Med.* **43**:133 (Jan.) 1940; Vitamin A: The Distribution of Vitamin A in the Body, *J. Mt. Sinai Hosp.* **7**:119 (Sept.-Oct.) 1940. Popper, H., and Greenberg, R.: Visualization of Vitamin A in Rat Organs by Fluorescence Microscopy, *Arch. Path.* **32**:11 (July) 1941.



of vitamin A, there was not much change in the hepatic cells, but the Kupffer cells were loaded with the vitamin and produced enough fluorescence for it to be visible to the unaided eye.

Popper and associates<sup>100</sup> extended these studies to observations on a series of specimens of human liver obtained either at autopsy or by biopsy. The content of vitamin A in the liver was reduced in acute hepatitis and in cirrhosis. A less marked degree of reduction was observed in obstructive jaundice. The degree of fluorescence of the Kupffer cells and of the parenchymal cells generally paralleled each other.

In localized areas of hepatic necrosis the necrotic area was free from vitamin A, while the Kupffer cells in the surrounding areas were rich in the vitamin. In toxic edema associated with sepsis, in uremia and in diabetes the Kupffer cells were strongly fluorescent, while the liver cells showed only traces of the vitamin. If the damage to the liver was severe, the Kupffer cells were free from the vitamin.

Tumors of the liver were found by Popper and Ragins<sup>101</sup> to show a moderate degree of fluorescence. The Kupffer cells in these same tumors all showed the presence of vitamin A. Hepatic metastases which were free of vitamin A at their primary site did not show the characteristic fluorescence, though the surrounding liver tissue was rich in vitamin A.

On the basis of these studies Popper suggests that the amount of vitamin A in the liver was determined primarily by the functional state of the hepatic cells. In all cases in which pathologic changes were present in the parenchyma of the liver the vitamin A was markedly reduced. In nearly all cases in which the amount of characteristic fluorescence was slight, evidence of damage to the hepatic cells was present. Pathologic changes in the periportal areas did not exert a decisive effect on the distribution of the vitamin. Nutritional effects on the amount of vitamin A in the liver were observed only after prolonged starvation or the administration of large doses of vitamin concentrate. Popper, therefore, concludes that the functional state of the liver is more important than nutritional influences in determining the amount of vitamin A in that organ. He also emphasizes the importance of the Kupffer cells in the metabolism of vitamin A and the evidence that in some cases of hepatic damage a block in the exchange of vitamin A between the Kupffer cells and the parenchymal cells of the liver is present.

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100. Popper, H.: Histological Distribution of Vitamin A in Human Organs Under Normal and Under Pathologic Conditions, *Arch. Path.* **31**:766 (June) 1941. Meyer, K. A.; Popper, H., and Ragins, A. B.: Histologic Distribution of Vitamin A in Biopsy Specimens of the Liver, *Arch. Surg.* **43**:376 (Sept.) 1941.

101. Popper, H., and Ragins, A. B.: Histologic Demonstration of Vitamin A in Tumors, *Arch. Path.* **32**:258 (Aug.) 1941.

# Editorial

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## TOXIC REACTIONS TO THE SULFANILAMIDE COMPOUNDS

Some of the most efficient therapeutic agents have undesirable side reactions even when judiciously employed. The sulfanilamide compounds are an example, although some reduction in the incidence of reactions has accompanied increased care in dosage and administration. Reactions following sulfanilamide therapy cannot apparently be altogether prevented. Now a group of investigators<sup>1</sup> claim to have devised a comparatively simple formula which is effective experimentally in reducing the toxic possibilities of sulfanilamide, sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) and sulfathiazole (2-[paraaminobenzene-sulfonamido]-thiazole) and yet does not result in a decrease in therapeutic efficacy.

The work which is reported in this issue of the ARCHIVES appears to be based on the assumption that detoxication in the body is obtained by oxidation, reduction and conjugation and that the principal compounds involved in this process are aminoacetic acid, choline, cystine, glucuronic acid, glutamine, sulfates, acetates and ornithine. Toxicity of sulfanilamide is ascribed to a sudden withdrawal of acetate precursors in the body during the process of conjugation by acetylation. Based on these concepts, the formula is intended to decrease the amount of acetylation by forcing conjugation into other channels, such as the formation of glucuronate.

Mice were used for toxicity studies, dogs for the determination of the rate of absorption and rats and rabbits for the measurement of the degree of conjugation. After trying the effects of various agents by oral administration, the authors concluded that calcium glucuronate was the most efficacious single compound and that a combination of aminoacetic acid, cystine, calcium glucuronate and ascorbic acid provided "the most consistent and the greatest protection." Their experiments convinced the investigators that loss of therapeutic efficacy does not occur when such agents are simultaneously administered with a sulfanilamide compound.

Knowledge of the pharmacologic and clinical possibilities of sulfanilamide and its derivatives is undeniably incomplete; available reports on

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1. Martin, G. J.; Fisher, C. V., and Thompson, M. R.: Therapeutic and Prophylactic Detoxication of Sulfanilamide, Sulfapyridine and Sulfathiazole, Arch. Int. Med., this issue, p. 662.

the prevention or diminution of toxic reactions following their use indicate that this aspect of study is even less complete. New communications based on animal or clinical investigations must therefore be critically considered from all points of view. Before the broad implications of this contribution are accepted, further substantiation under carefully controlled experimental conditions is obviously desirable.

## News and Comment

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**The Herman M. Biggs Memorial Lecture.**—Dr. James S. McLester, Professor of Medicine at the University of Alabama, Chairman of the Council on Foods and Nutrition of the American Medical Association and Chairman of the Subcommittee on Medical Nutrition of the National Research Council, delivered the Herman M. Biggs Memorial Lecture on Thursday, April 2, at Hosack Hall, the New York Academy of Medicine, under the auspices of the Committee on Public Health Relations.

His subject was "Nutrition and the Nation at War."

**American Heart Association.**—The eighteenth scientific meeting of the American Heart Association will be held June 5 and 6, 1942, at Chalfonte-Haddon Hall, Atlantic City, N. J.

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### CORRECTIONS

On page 278 of the review "Diseases of Nutrition" by Drs. Butt, Leary and Wilder in the February issue (ARCH. INT. MED. **69**:277, 1942) the manner of citation of a paper by Wolbach and Bessey (Vitamin A Deficiency and the Central Nervous System, Am. J. Path. **17**:586 [July] 1941) implied that these authors stated vitamin A deficiency causes overgrowth of skeletal tissues. Actually they reported that in vitamin A deficiency in rats skeletal growth is retarded earlier than growth of the soft tissues in general, including that of the central nervous system. They have shown that in the white rat at least the nervous manifestations are due to pressure effects caused by the relative overgrowth of the central nervous system.

In the article by Drs. Rosenberg, Dockerty and Meyerding entitled "Coccidioid Arthritis: Report of a Case in Which the Ankles Were Involved and the Condition Was Unaffected by Sulfanilamide and Roentgen Therapy," in the February issue (ARCH. INT. MED. **69**:238, 1942), in the heading for table 1, on page 242, "Acute Granulomatous Coccidioidomycosis" should read "Chronic Granulomatous Phase of Coccidioidomycosis."

## Book Reviews

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**Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases.** By Richard P. Strong, M.D., Professor of Tropical Medicine, Emeritus, Harvard University. Sixth edition, 2 volumes. Price, \$21. Pp. lix + 1,747, with 398 illustrations. Philadelphia: P. Blakiston's Son & Company, 1942.

In 1914 Admiral Stitt prepared a modest handbook on tropical diseases. It was only 421 pages long, was simply written and, as *The Journal of Tropical Medicine and Hygiene* reported (18:96 [April 15] 1915), was so planned that students could visualize the subject from every angle.

The book was deservedly popular, so that new editions were necessary every few years. The fifth edition was printed in 1929. It had kept pace with advancing knowledge and was 918 pages long. The author, however, succeeded in maintaining the book's character and charm. *The Journal of Tropical Medicine and Hygiene*, which had studied each edition carefully, was glad to point out that even though fifteen years old, Stitt's "Tropical Diseases" could still be recommended as a reliable guide to all members of the medical profession (32:172 [June 15] 1929).

The sixth edition is more elaborate than its predecessors and appears in two volumes; each is 850 pages long. The book has changed hands to a certain extent, for the first five editions represented the views of the United States Army, Navy and Public Health Service on tropical medicine, whereas the sixth edition emanates from the Department of Tropical Medicine of Harvard University.

Admiral Stitt and Dr. Strong are close friends of more than forty years' standing. One suspects that they have studied tropical medicine together, have seen eye to eye on many subjects and have watched the growth of knowledge in their favorite medical field with justifiable pride. Therefore, the new author of the sixth edition of Stitt's "Tropical Diseases" carries forward skilfully the same philosophy which made the earlier editions so successful and through his method of writing adds color to the blue and gold of the Navy by a dash of Harvard crimson without in any way hurting the original product.

The format of the two volumes is excellent. The illustrations are clear. More attention now is paid to current literature, so that at the end of each section has been added a trustworthy bibliography, which will appeal to the student. The arrangement of subject matter is much as it was in earlier editions. Diseases caused by protozoa, bacteria and filterable viruses are well described. There are interesting chapters on nutritional disorders of the tropics and on diseases caused by fungi, plants, animals or unrecognized agents. There is so much more to be told of prevention of disease in the tropics and of tropical hygiene than heretofore that the title of the book has been changed to lay emphasis on this fact.

It must be gratifying to two such old friends as are Admiral Stitt and Dr. Strong to have so fine a book evolve from their combined efforts. It must be even more gratifying for them to realize that this new edition was ready at a time when such a comprehensive manual would be seized on by, be studied by and be useful to vast numbers of those very men whom they always have found most congenial—the soldiers, sailors and public health officers whose job it is to meet medical problems under field conditions in all the warm corners of the earth.

**Beiträge zur Röntgendiagnostik der Otitis Media Acuta und ihrer Komplikationen im Schläfenbein.** By Sölve Welin, from the Diagnostic Division of the Otolaryngological Clinic of the University of Lund. Acta radiol., supp. XLII. Price, 20 kronor. Pp. 180, with 105 illustrations. Lund, Sweden: Håkan Ohlsson Boktryckeri, 1941.

This monograph is a contribution to the study of the importance of the clinical investigation of acute otitis media. Especially when the clinical findings are

indecisive, roentgen research often supplies the necessary data for determining whether there exists a pathologic change in the bone and whether this change is significant. This study is based on 926 patients seen between 1934 and 1939 whose conditions were given a diagnosis of otitis media. Of this group, 226 patients had bilateral acute inflammation of the middle ear, 338 had an inflammation only on the right side and in 362 the condition was confined to the left side.

Of especial practical value is the chapter on technic, which contains detailed instructions for the positions advocated by Henle, Schüller, Lange, Sonnenkalb, Mayer, Altschul, Stenvers and Runström. Still other positions might have been utilized, but these are the most informative. In each instance the positions are illustrated by lucid drawings and well reproduced roentgenograms. An excellent chapter deals with roentgen anatomy in children and adults. Other chapters discuss the roentgen pathology of indeterminate or obliterated intercellular structures, classified according to the lime content and all generously illustrated by typical cases. Special attention is given to labyrinthitis, perisinal abscess and apicitis, with all of which the roentgen findings are practically indispensable. An elaborate bibliography terminates the book.

**Treatment of the Patient Past Fifty.** By Ernst P. Boas. Price, \$4. Pp. 324, with 19 illustrations. Chicago: The Year Book Publishers, Inc., 1941.

The reviewer has no criticism of this book, which is well written by a man who obviously knows what he is talking about; he does, however, have a considerable doubt as to the need of a separate book on the medical treatment of the aged. After all, no new principles are invoked, and one really deals with a purely artificial division if one separates people into those over and those under 50. One discerns in all this the lush tendency to overdo, to specialize artificially and in other ways to make medicine as cumbersome and complicated as possible which seems to have caught every one nowadays. Followed to its logical conclusion, this idea may in the end produce books on the medical treatment of adolescents, of young adults, of persons in the middle decades, etc., etc.—clearly a reduction to absurdity.

**About Ourselves.** By James G. Needham, Ph.D. Price, \$3. Pp. 269, with illustrations. Lancaster, Pa.: Jaques Cattell Press, 1941.

This volume is what the author says it is—a survey of human nature from the zoologic viewpoint. It is an “exposition of human nature without any plans for its improvement.”

In Part I—Man in His Biological Aspects—are discussed such matters as factors common to all living things, man's ancestry, development of behavior, instinct, learning and man in his environment.

Part II—Society in Its Biological Aspects—consists of a discussion of the components of social behavior, the components being physiologic activities, instincts, customs and reason. These component parts are also discussed in relation to war, government and religion.

The subject matter, though complex in nature, is simply given and is such that it will be comprehended and enjoyed by the reader, lay or professional.

**Roentgen Treatment of Infections.** By James F. Kelly and D. Arnold Dowell. Price, \$6. Pp. 432, with 122 figures and 25 tables. Chicago: The Year Book Publishers, Inc., 1942.

The actual discussion of treatment of infections is preceded by chapters on roentgen rays and roentgen therapy in general which are concise and well written. Infection is discussed in great detail, and there is a good deal of material which is somewhat beside the subject. The writers are clearly enthusiastic supporters of radiation therapy of infections. However, their suggestion that it may be more useful than therapy with sulfanilamide or any of its derivatives (page 381) is

perhaps open to argument, and the enthusiasm of the writers for roentgen therapy of rheumatoid arthritis and various other conditions is not entirely supported by the reviewers experience.

**Infant Nutrition.** By Williams McKim Marriott and P. C. Jeans. Third Edition. Price, \$5.50. Pp. 475, with 31 illustrations. St. Louis: C. V. Mosby Company, 1941.

The addition to knowledge of infant nutrition has been so great in the last few years that Dr. Jeans has appropriately taken on himself the duty of reediting this standard textbook. The chapters on growth and development and on metabolism are well written, and the new knowledge is brought out in fairly simple fashion, so that the text is not confusing to the medical student or the general practitioner, the readers to whom it would most appeal. The book answers satisfactorily many of the questions that mothers ask about their babies and tells what to do in the correction of many minor, but to the household in which a baby lives very important, ailments.

**The Treatment of Burns.** By Henry S. Harkins. Price, \$6.50. Pp. 457, with 120 figures. Springfield, Ill.: Charles C. Thomas, Publisher, 1942.

The reviewer's first thought was how can there be enough to say about burns to fill such a large volume, but on going through the book one finds no superfluous material. The writer has achieved a monograph of the first order, scholarly, well arranged, dealing with every phase of the subject and documented by no less than thirteen hundred and twenty references. The work is richly illustrated by every conceivable sort of chart and diagram and many graphic pictures of clinical cases. In view of the war, this monograph seems especially timely.

**Diabetes Mellitus.** By Zolton T. Wirtschafter and Morton Korenberg. Price, \$2.50. Pp. 186, with 9 figures and 3 tables. Baltimore: Williams & Wilkins Company, 1942.

This little book on diabetes is different from most similar productions, in that it deals almost altogether with the pathologic physiology of the disease. While many controversial questions are discussed, the position of the writer seems to be sound and the material is well documented with a bibliography of several hundred references. The book should be of great use in supplementing the ordinary clinical treatises.

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## INDUCED THIAMINE (VITAMIN B<sub>1</sub>) DEFICIENCY AND THE THIAMINE REQUIREMENT OF MAN

FURTHER OBSERVATIONS \*

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In earlier studies<sup>1</sup> a group of 4 subjects was maintained for 147 days and another group of 4 subjects for 88 days on a diet containing not more than 0.15 mg. of thiamine (0.07 mg. for each 1,000 calories of the standard diet). This provision of thiamine represented a restriction to little more than a sixth of the amount of thiamine considered at the time to be the minimal daily requirement.<sup>2</sup>

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\* Presented in abstract to the American Institute of Nutrition, Chicago, April 16, 1941. A preliminary report of this study has been published (Williams, R. D., and Mason, H. L.: Further Observations on Induced Thiamine [Vitamin B<sub>1</sub>] Deficiency and Thiamine Requirement of Man: Preliminary Report, Proc. Staff Meet., Mayo Clin. **16**:433-438 [July 9] 1941).

1. Williams, R. D.; Mason, H. L., and Smith, B. F.: Induced Vitamin B<sub>1</sub> Deficiency in Human Subjects, Proc. Staff Meet., Mayo Clin. **14**:787-793 (Dec. 13) 1939. Williams, R. D.; Mason, H. L.; Wilder, R. M., and Smith, B. F.: Observations on Induced Thiamine (Vitamin B<sub>1</sub>) Deficiency in Man, Arch. Int. Med. **66**: 785-799 (Oct.) 1940.

2. The minimal daily requirement of thiamine for a man was set by the Technical Commission of the League of Nations Health Committee (Report by the Technical Commission on Nutrition on the Work of Its Third Session, Bull. Health Organ., League of Nations **7**:460-502 [June] 1938) at 300 international units (0.9 mg.). The minimal daily requirement for thiamine for a man recently promulgated by the Food and Drug Administration of the Federal Security Agency

(Footnote continued on next page)



The disease induced by this severe, isolated restriction of thiamine minutely resembled in the early stages the disturbance which commonly is known as "anxiety neurosis," but which the discriminating psychiatrist designates as "neurasthenia." At the end of the period of deprivation of thiamine the clinical picture was that of anorexia nervosa. Inactivity, apathy, serious derangement of metabolic processes, loss of weight and, finally, prostration, were observed in all subjects. None of these signs and symptoms developed in other subjects who received an identical diet supplemented with not less than 0.95 mg. of thiamine hydrochloride administered in disguised forms. This provided a total intake of 1.1 mg. of thiamine.

The severe restriction of thiamine in these earlier studies and the attendant loss of body weight induced a syndrome which undoubtedly is encountered infrequently in clinical practice. Such extreme deprivation of this vitamin would be unlikely to occur in a population at large. Therefore, in the study now being reported the intake of thiamine was restricted only to 0.45 mg. (0.22 mg. per thousand calories of the diet), an amount not much if any below that provided by the "poor" diets reported in the Stiebeling-Phipard<sup>3</sup> survey of purchases of food by American families.

#### METHODS

The nutrition division of the Rochester State Hospital, in which these studies have been conducted, consists of a diet kitchen, utility rooms and room space for twenty beds. It is isolated from the rest of the hospital. Three nurses, a dietitian, a laboratory assistant and a physician devote full time services to investigation.

Persons for study are selected tentatively, transferred to the division and provided with an ample diet so that a good nutritional status can be assured. During this period of several weeks or months they become familiarized with ward routines and analytic procedures and are closely observed prior to their final selection.

After such a period of preliminary observation 11 white women between the ages of 23 and 46 years were chosen as subjects for the experiments reported here. The selection was made on the basis of their willingness and ability to cooperate, absence of a history of recent abnormal nutrition and absence of significant manifest

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(Federal Register, Nov. 22, 1941) was 333 international units (1.0 mg.). The daily allowances of thiamine recommended by the Committee on Food and Nutrition of the National Research Council (Recommended Daily Allowances for Specific Nutrients, Medical Preparedness, J. A. M. A. **116**:2601 [June 7] 1941), accepted by the National Nutrition Conference for Defense (The National Nutrition Conference, Pub. Health Rep. **56**:1233-1255 [June 13] 1941) meeting in Washington, D. C., May 26-28, 1941, were 1.8 mg. for a moderately active man, 1.5 mg. for a sedentary man, 1.5 mg. for a moderately active woman and 1.2 mg. for a sedentary woman.

3. Stiebeling, H. K., and Phipard, E. F.: Diets of Families of Employed Wage Earners and Clerical Workers in Cities, Circular 507, United States Department of Agriculture, January 1939.

physical or emotional abnormalities.<sup>4</sup> The subjects had been, and under direct supervision, continued to be engaged in various activities of the ward, such as housekeeping, laundering and sewing. Activity up to reasonable limits of ability was encouraged.

The intake of thiamine of all 11 subjects was decreased for a period of 132 days, during which reactions to the restricted regimen were determined. The subjects then were divided into two groups. The first group of 5 served for study of more prolonged thiamine deficiency; the second group of 6 served for study of thiamine requirements. Progressively increasing amounts of thiamine hydrochloride were administered in disguised form to the subjects of the latter group. Since the environment and with the exception of the supplement of thiamine hydrochloride the dietary regimens of the two groups were identical, the second group served in some degree as a control for the first. However, we believed that the great variation in biologic material in groups of human subjects makes this type of control unreliable. Therefore, we have attributed to thiamine deficiency only such signs, symptoms and metabolic defects as have appeared on restriction of thiamine and disappeared within a reasonable period when thiamine hydrochloride was provided in amounts sufficient for repletion of tissue stores. Thus, in addition to control of group 1 by group 2, each subject served as her own control.

The standard diet given to all subjects was composed exclusively of foods which commonly appear on American tables. It comprised white bread, corn flakes, potatoes, polished rice, sucrose, skimmed milk, beef, cheese, egg white, gelatin, butter, vegetable fat, canned fruits, canned vegetables, coffee and cocoa. Special attention was given to the appearance and palatability of the foods served. The thiamine content of each food used, as well as that of the composite diet, was determined by the thiochrome method as modified by Hennessy.<sup>5</sup> Large stores of food, together with standardized technics of cooking them, made it possible to secure such uniformity that daily variations in the thiamine content of the standard diet as prepared did not exceed 0.04 mg. The standard diet<sup>6</sup> (table 1) provided 0.22 mg. of thiamine for each 1,000 calories.

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4. The basal metabolic rate of subject 11 was + 20 per cent, and that of subject 10 was — 17 per cent. All subjects had been under treatment for psychiatric abnormalities. They were, however, "recovered" and fully capable of exercising a decision in volunteering for this service. In addition, the consent of relatives and guardians was always secured. Possible criticism of these studies on the ground that patients "recovered" from mental disease might be expected to experience psychiatric disturbances from any change of environment or any nutritional deficiency is answered by the conditions of the control. Every experiment involved a long foreperiod, a long period of restriction of thiamine and a long afterperiod. Only among those subjects deprived of thiamine did the abnormalities we are attributing to thiamine deficiency develop, and they responded to treatment with thiamine, administered without their knowledge, by full and complete recovery from the abnormalities in question. Furthermore, these abnormalities did not develop among other groups of subjects deprived of riboflavin but not of thiamine and maintained in the same environment. The studies of deficiency of riboflavin are in progress and will be reported later.

5. Hennessy, D. J.: Chemical Method for Determination of Vitamin B<sub>1</sub>, *Indust. & Engin. Chem. (Analyt. Ed.)* **13**:216-218 (April 15) 1941.

6. Chatfield, C., and Adams, G.: Proximate Composition of American Food Materials, Circular 549, United States Department of Agriculture, June 1940.

The caloric intake was adjusted to the requirement of each subject by the giving of larger or smaller servings of the standard diet. Selection of one food on the tray and refusal of another was not permitted. By this means the ratio of thiamine to calories was held nearly constant. Approximately 60 per cent of the calories were derived from carbohydrate, 14 per cent from protein and 26 per cent from fat. To provide, so far as could be judged, an ample supply of iron and calcium and complete adequacy of vitamins other than thiamine, the diet was supplemented with 20.0 Gm. of autoclaved brewers' yeast, 0.1 Gm. of halibut liver oil with irradiated ergosterol (5,000 international units of vitamin A and 1,000 international units of vitamin D), 80 mg. of ascorbic acid, 0.2 Gm. of exsiccated

TABLE 1.—*Composition of Standard Diet* \*

Food	State of Preparation	Grams				Calories
		Amount	Carbo-hydrate	Protein	Fat	
Bread .....	Special recipe	180	94	15	4	472
Butter .....	As purchased	30	....	....	24	216
Skim milk powder.....	Served as 10% solution	20	10	7	....	68
Cornflakes .....	As purchased	15	12	1	....	52
Beef (rib cut) .....	Roasted	75	....	23	11	191
Potato .....	Baked	75	14	2	....	64
Cheese, American cheddar .....	As purchased	30	....	8	10	122
Polished rice, dry...	Boiled or steamed	33	26	3	....	116
Gelatin .....	Special recipe	100	15	2	....	68
Apple jelly .....	Commercial	20	14	....	....	56
String beans .....	Canned	75	3	1	....	16
Carrots .....	Canned	50	4	1	....	20
Peaches .....	Canned	130	24	1	....	100
Pears .....	Canned	130	24	....	....	96
Sugar .....	As purchased	30	30	....	....	120
Candy .....	Special recipe	20	19	....	....	76
Cake or cookies.....	Special recipe	40	22	2	5	141
Total (by calculation) .....			311	66	54	1,994

\* The content of thiamine was approximately 0.2 mg. per thousand calories. The standard diet was supplemented by 0.1 Gm. of halibut liver oil with irradiated ergosterol (5,000 international units of vitamin A, 1,000 international units of vitamin D); 20 Gm. of brewers' yeast (autoclaved); 80 mg. of ascorbic acid; 0.2 Gm. of ferrous sulfate, exsiccated, and 0.6 Gm. of tricalcium phosphate.

ferrous sulfate and 0.6 Gm. of tricalcium phosphate. All subjects subsisted on this regimen continuously from July 25, 1940 to June 1, 1941, and evidence of deficiency of riboflavin, nicotinic acid, ascorbic acid or vitamin A or of any deficiency not attributable to thiamine was not observed in any of them at any time.

The urine of every subject was analyzed for thiamine not less frequently than once a week. The method of Hennessy and Cerecedo was employed. These analyses not only served as an index of the degree of deprivation of thiamine; they provided a check or control of the intake of thiamine.

Body weight, physical and neurologic signs and symptoms, tolerance for exercise, electrocardiographic changes, size of heart as determined by roentgen examination, gastric analysis, dextrose tolerance, values for sugar  $\tau$  in blood drawn while the

7. Miller, B. F., and Van Slyke, D. D.: A Direct Microtitration Method for Blood Sugar, *J. Biol. Chem.* **114**:583-595 (July) 1936.

subjects were fasting and for serum protein,<sup>8</sup> blood content of pyruvic acid<sup>9</sup> and lactic acid,<sup>10</sup> serum calcium and phosphorus, basal metabolic rates and gastrointestinal motility were determined periodically on every subject. These examinations were made (1) during the period of preliminary observation, (2) during a subsequent period of restriction of thiamine and (3) again during a recovery period, in which the administration of thiamine was the only change in the regimen. The estimates of gastrointestinal motility were based on roentgen examinations made at intervals for thirty minutes and roentgenograms made half an hour and one, two, three and five hours after ingestion of a barium sulfate meal.

## RESULTS

*Observations in the Period in Which the Diet Was Deficient in Thiamine.*—Restriction of thiamine was begun on July 25, 1940. Disturbing symptoms necessitating administration of thiamine developed in 1 instance (subject 11, table 2) in 89 days. However, in 3 cases (subjects 1, 2 and 3) the restriction of thiamine could be continued for 131 days, in 5 (subjects 4, 5, 6, 7 and 8) for 169 days and in 2 (subjects 9 and 10) for 196 days.

The apparent<sup>11</sup> amounts of thiamine in the urine in most cases decreased within 30 days to low levels of 15 to 30 micrograms daily. The time of onset of signs and symptoms of deficiency of thiamine varied. In general, the more active subjects were the first to reveal evidence of abnormality. The most conspicuous of the early abnormalities observed in all subjects after 8 to 12 weeks of restriction of thiamine were gross changes of behavior, marked changes of attitude, diminished inclination to perform accustomed tasks and progressive decrease of ability to make social adjustments within the group. A summary of the daily intake of food, intake and excretion of thiamine and the clinical status of representative subjects during the period of preliminary observation, during the period of restricted intake of thiamine and during subsequent periods in which the diet, restricted in content of thiamine, was supplemented with thiamine hydrochloride is presented in tables 2, 3, 4, 5 and 6.

It should be emphasized that these were unmistakable, easily demonstrated changes of personality, which were reflected in attitude, behavior and effectiveness in performing tasks which previously had been performed readily. All subjects became irritable, depressed, quarrelsome,

8. Kingsley, G. R.: A Rapid Method for the Separation of Serum Albumin and Globulin, *J. Biol. Chem.* **133**:731-735 (May) 1940.

9. Bueding, E., and Wortis, H.: The Stabilization and Determination of Pyruvic Acid in the Blood, *J. Biol. Chem.* **133**:585-591 (April) 1940.

10. Barker, S. B., and Summerson, W. H.: The Colorimetric Determination of Lactic Acid in Biological Materials, *J. Biol. Chem.* **138**:535-554 (April) 1941.

11. Mason, H. L., and Williams, R. D.: The Effect of Ingestion of Nicotinic Acid on the Determination of Thiamine in Urine by the Thiochrome Method, *J. Biol. Chem.* **140**:417-422 (Aug.) 1941.

TABLE 2.—Restriction of Thiamine from July 25 to Oct. 22, 1940 in Subject 11, a Woman Aged 29, 154 Cm. Tall

Period of Study	Diet				Thiamine Hydrochloride Supplement, Micrograms	Thiamine, Micrograms	Dietary Supplement, Micrograms*	Thiamine Excreted in Urine, Micrograms	Body Weight, Kg.	Clinical Status of Subject †
	Carbohydrate	Protein	Fat	Calories						
Preliminary	247	56	71	1,851	783			75	49.2	Cheerful, industrious, careful worker; blood pressure 117/85; pulse rate 85; basal metabolic rate + 20% (subtotal thyroidectomy); 4,500,000 erythrocytes; fatigued, irritable, restless by end of period
July 25, 1940 to August 26	263	54	54	1,754	415			29	47.9	Complains of insomnia, fatigue, soreness of muscles, "eye strain," giddiness, inability to concentrate on plan work, backache; bewildered, apprehensive; does little work; blood pressure 100/70; pulse rate 65; faint heart sounds; pallor and giddiness on standing; reduced exercise tolerance; basal metabolic rate + 16%; 4,120,000 erythrocytes
August 27 to September 24	241	50	50	1,614	376			11	45.5	Complains of anorexia, epigastric pain, fatigue, soreness of muscles, dyspnea and palpitation on exertion, failing memory; displays emotional instability, irritability, quarrelsomeness, vacillation, bewilderment; does no work; blood pressure 100/50; pulse rate 67; vasomotor hypotonia; basal metabolic rate + 6%; 3,600,000 erythrocytes
September 25 to October 21	323	60	57	2,045	467		1	12	45.5	Complains of fatigue, nausea, headache, hot flushes, giddiness, muscular pains; irritable, quarrelsome, demanding, defiant; elevated blood pyruvate; blood pressure 100/60; pulse rate 68; P2>A2; pallor and swaying on standing; basal metabolic rate + 2%; 3,600,000 erythrocytes
October 22 to November 24	314	60	56	2,000	454	3,000 15,000 2,500		649 2,400 670	45.5	Moderate improvement; cooperative; does some work but is awkward and inefficient and tires quickly; complains of anorexia, epigastric pain, headache; blood pressure 95/55; pulse rate 78; heart sounds stronger; no pallor or swaying on standing; basal metabolic rate — 3%; 3,480,000 erythrocytes
November 25 to December 24	340	62	58	2,130	450	3,000	2	670	45.8	Further improvement; excellent appetite most of time; congenial; works vigorously for short periods and is efficient and careful worker; mood is labile, with an occasional tantrum; blood pressure 100/70; pulse rate 76; prompt vasomotor responses to position; basal metabolic rate + 3%; 3,320,000 erythrocytes
December 25 to Jan. 30, 1941	280	55	54	1,826	404	2,000	2 3 4 5	800	45.5	Improvement in general appearance and record of work; much more active, usually cooperative and congenial; tantrum after failure of plans for going home; blood pressure 98/65; pulse rate 80; no abnormal vasomotor phenomena; reflexes hyperactive; basal metabolic rate + 7%; 3,160,000 erythrocytes
January 31 to February 25	.....	....	....	.....	.....	2,000	6	.....	48.8	Alert, cheerful, industrious; ability for physical exertion steadily increasing; consistently good appetite; no physical defect; basal metabolic rate + 13%; 3,960,000 erythrocytes

\* The following dietary supplements (other than thiamine hydrochloride and basal supplements) were given for study of anemia associated with restriction of thiamine: (1) 50 mg. of pyridoxine, 100 mg. of calcium pantothenate, 12 mg. of riboflavin and 100 mg. of nicotinic acid daily from Sept. 23 to Oct. 20, 1940; (2) 20 mg. of unautoclaved brewers' yeast daily from Dec. 4, 1940 to Jan. 6, 1941; (3) a total dose of 105 cc. (105 U. S. P. units) of crude liver extract administered parenterally from Dec. 24, 1940 to Jan. 8, 1941; (4) a total dose of 150 Gm. of liver concentrate (1:20) administered orally from Jan. 15 to Jan. 30, 1941; (5) 1.0 Gm. of choline chloride daily from Jan. 25 to Jan. 30, 1941, and (6) a total dose of 450 U. S. P. units of purified liver extract (15.0 U. S. P. units per cubic centimeter) from Jan. 30 to Feb. 25, 1941.

† The clinical notes apply to the condition of the subject at the end of the period to which they are appended.

TABLE 3.—*Restriction of Thiamine from July 25, 1940 to Jan. 13, 1941 in Subject 4, a Woman Aged 23, 172 Cm. Tall\**

Period of Study	Diet				Thiamine Hydrochloride Supplement, Micrograms	Thiamine Excreted in Urine, Micrograms	Body Weight, Kg.	Clinical Status of Subject †
	Grams			Thiamine, Micrograms				
	Carbohy- drate	Pro- tein	Fat					
Preliminary	278	60	75	2,027	856	.....	90	Asymptomatic, well adjusted to regimen, congenial, industrious, efficient, vigorous; basal metabolic rate 0.0%; 4,900,000 erythrocytes
July 25, 1940 to September 23	335	62	57	2,101	466	.....	11	Works slowly; neglects work; follows instructions inaccurately; forgetful, irritable, quarrelsome; appetite capricious; basal metabolic rate — 23%
September 24 to November 18	378	64	65	2,353	475	.....	24	Weeps and laughs alternately; self depreciatory; displays apathy, confusion, fatigue; works irregularly; complains of formication, pain in epigastrium, numbness of hands and feet; basal metabolic rate — 16%; frequent emesis
November 19 to Jan. 13, 1941	403	62	82	2,598	482	.....	- 28	Unable to work because of dizziness and weakness; displays hopeless attitude; confused, bewildered, vacillating with apathy alternating with agitation, depressed; blood pressure 98/65; pallor and giddiness on standing; T waves of lead Cr-2 inverted; premature systoles; hands and feet cold and mottled; basal metabolic rate — 14%
January 14 to February 27	405	63	85	2,637	480	200 400	51 101	Continues to be depressed, restless, worried, definitely less apathetic; does not grasp instructions; displays lack of dexterity; appetite capricious with occasional emesis; insomnia; blood pressure 110/72; no pallor or giddiness on standing
February 28 to April 4	400	63	86	2,626	484	600 800	190 202	Gradual improvement; assists with ward work; tires easily; cheerful at times, apathetic at others; sleeps fitfully; appetite consistently good; basal metabolic rate — 24%
April 5 to May 2	366	62	85	2,477	486	1,000 1,200	287 557	Congenial, cooperative, industrious; works more vigorously; no complaints, no physical defects; basal metabolic rate — 24%
May 3 to May 30	360	63	66	2,286	480	1,400 1,600	589 730	Asymptomatic, agreeable, efficient, vigorous; basal metabolic rate — 19%; 4,270,000 erythrocytes

\* This is one of the subjects who were given large doses of thiamine hydrochloride prior to the study of thiamine requirements.  
† The clinical notes apply to the condition of the subject at the end of the period to which they are appended.

TABLE 4.—*Restriction of Thiamine from July 25, 1940 to Dec. 3, 1940 in Subject 2, a Woman Aged 33, 158 Cm. Tall\**

Period of Study	Diet				Thiamine Hydrochloride Supplement, in Urine, Micrograms	Thiamine Excreted in Urine, Micrograms	Body Weight, Kg.	Clinical Status of Subject †	
	Grams			Thiamine, Micrograms					
	Carbohy- drate	Pro- tein	Fat						Calories
Preliminary	290	60	72	2,048	850	.....	128	49.2	Asymptomatic, cooperative, congenial, industrious, engaged in ward housekeeping; basal metabolic rate +11%; 4,500,000 erythrocytes
July 25, 1940 to October 21	338	62	57	2,113	457	.....	18	48.6	Irritable, quarrelsome, uncooperative; lack of initiative; neglects duties; activity reduced; complains of numbness of feet, aching of muscles, epigastric pain, anorexia, constipation; blood pressure 95/65; pulse rate 60; A2>P2; basal metabolic rate — 3%
October 22 to December 2	325	60	57	2,053	462	.....	20	49.6	Uncooperative, defiant, inactive; lacks initiative; complains of anorexia, epigastric pain, dyspnea on exertion, insomnia; blood pressure 90/50; pulse rate 68; giddiness and pallor on standing; faint heart sounds; premature systoles; QT interval 0.40 sec.; 4,200,000 erythrocytes
December 3 to Jan. 9, 1941	333	59	55	2,063	460	3,000 7,500	1,400	50.4	Congenial, cooperative; resumes duties in ward; careful of appearance, "feels good"; minimal tenderness of muscles of calves; blood pressure 110/75; heart sounds stronger; brady- cardia; basal metabolic rate — 9%
January 10 to February 6	352	60	57	2,161	462	..... 200	386 134	50.5	Activity reduced; loss of interest; begins many tasks but finishes few of them; complains of anorexia, fatigue, paresthesia of feet, soreness of muscles; blood pressure 95/75; pulse rate 56; basal metabolic rate — 23%; QT interval 0.44 sec.
February 7 to March 18	334	53	60	2,108	451	400 600	125 215	50.3	Energetic, cheerful; sleeps soundly; appetite good; no complaints; blood pressure 115/75; pulse rate 70; basal metabolic rate — 23%; 4,050,000 erythrocytes; QT interval 0.42 sec.; marked sinus arrhythmia
March 19 to April 18	325	59	57	2,049	446	800 1,000	238 308	51.0	Asymptomatic; no physical defect; basal metabolic rate — 6%
April 19 to May 30	322	61	56	2,036	452	1,200 1,400 1,600	498 547 786	50.4	Greater energy; industrious, vigorous; blood pressure 115/75; pulse rate 80; no physical defect; basal metabolic rate — 8%; 4,280,000 erythrocytes

\* This is one of the subjects who were given large doses of thiamine hydrochloride prior to the study of thiamine requirements.  
† The clinical notes apply to the condition of the subject at the end of the period to which they are appended.

TABLE 5.—*Restriction of Thiamine from July 25, 1940 to Jan. 10, 1941 in Subject 8, a Woman Aged 46, 161 Cm. Tall*

Period of Study	Diet				Thiamine Hydrochloride Supplement, Micrograms	Thiamine Excreted in Urine, Micrograms	Body Weight, Kg.	Clinical Status of Subject †	
	Grams			Thiamine, Micrograms					
	Carbohydrate	Protein	Fat						
Preliminary	255	60	72	1,908	850	..	64	45.0	Asymptomatic; moderately active in ward housekeeping; basal metabolic rate +5%; 4,500,000 erythrocytes
July 25, 1940 to September 24	301	60	56	1,948	464	..	9	45.1	Ceases working; only interest is reading; complains of anorexia, indigestion; eats only after urging; weeps after exercise tolerance test; blood pressure 85-95/58; tachycardia; faint heart sounds; basal metabolic rate — 10%
September 25 to November 18	318	62	58	2,042	460	..	22	46.2	Apathetic, confused, bewildered, vacillating, forgetful; appetite capricious with episodes of nausea and emesis; inactivity; hands and feet cold and mottled; tenderness of muscles of calves; basal metabolic rate +3%; 3,630,000 erythrocytes
November 19 to Jan. 9, 1941	280	51	48	1,756	415	1	25	47.8	Fearful, delayed, uncertain responses; rests on bed; appetite poor; complains of epigastric pain, backache, headache, soreness of muscles, dyspnea; pallor and swaying on standing; patellar and achilles tendon reflexes exaggerated; blood pressure 85-95/50; pulse rate 72; P2>A2
January 10 to February 10	269	52	50	1,734	412	..	686 .....	47.0	Increase of activity; careful of appearance; works occasionally but is easily fatigued; memory somewhat improved; blood pressure 95/65; pulse rate 68; heart sounds stronger; basal metabolic rate —18%; 4,260,000 erythrocytes
February 11 to March 24	298	61	59	1,967	463	..	.....	46.7	Gradual improvement; less easily fatigued; does some work, attentive to personal appearance; no physical defects, no complaints; basal metabolic rate — 2%; 3,910,000 erythrocytes
March 25 to April 27	273	57	55	1,815	444	2	.....	47.8	Further improvement, greater activity; more alert; appetite good, memory greatly improved; no complaints; blood pressure 105/75; heart sounds of good quality; basal metabolic rate 0.0%
April 28 to May 30	.....	....	....	.....	.....	2	.....	48.1	Volunteers for work; memory fairly accurate; general appearance much improved; no complaints; basal metabolic rate +7%; 4,360,000 erythrocytes

\* The following dietary supplements (other than thiamine hydrochloride and the basal supplements) were given for study of the anemia associated with restriction of thiamine: (1) rice polish concentrate "Factor II" from Dec. 24, 1940 to Jan. 6, 1941, and (2) choline chloride from April 10 to May 14, 1941.

† The clinical notes apply to the condition of the subject at the end of the period to which they are appended.



TABLE 6.—*Restriction of Thiamine from July 25, 1940 to Feb. 6, 1941 in Subject 10, a Woman Aged 41, 173 Cm. Tall*

Period of Study	Diet				Thiamine Hydro- chloride Supple- ment, Micro- grams	Thiamine Excreted in Urine, Micro- grams	Body Weight, Kg.	Clinical Status of Subject †	
	Grams			Calories					
	Carbo- hydrate	Pro- tein	Fat						
Preliminary	273	60	72	1,980	850	.....	..	57	Well adjusted to ward, cooperative, industrious, congenial; assists with ward housekeeping, sews, sings in choir; blood pressure 128/85; pulse rate 82; basal metabolic rate — 17%; 5,000,000 erythrocytes
July 25, 1940 to September 20	330	61	57	2,077	460	.....	..	10	Works less vigorously but is competent and industrious; weeps frequently; no complaints; blood pressure 130/90; pulse rate 65; tendon reflexes hyperactive; basal metabolic rate — 22%
September 21 to November 15	385	63	62	2,350	470	.....	..	22	Complains of weakness, tenseness, hot and cold flushes, giddi- ness, numbness of feet and hands; irritable, depressed, self conscious; refuses choir practice; bedraggled appearance; blood pressure 100/58; pulse rate 71; pallor and swaying on standing; cold mottled hands and feet; P2>A2; weak heart sounds; 3,920,000 erythrocytes; basal metabolic rate — 15%
November 16 to December 14	392	62	81	2,545	481	.....	1 2	32	No new complaints; depressed, confused, apprehensive, easily fatigued; labile blood pressure 127/85-110/75; pulse rate 77; marked sinus arrhythmia; tachycardia on slight exertion; P2>A2; 3,700,000 erythrocytes
December 15 to Jan. 10, 1941	425	62	84	2,944	489	.....	1 2 3 4	41	Complains of weakness, weariness, pains in legs, epigastric pain, dyspnea on exertion; despondent, distraught, vacillating, forgetful, inefficient; harrassed appearance; labile blood pressure and pulse rate; sinus arrhythmia and tachycardia; basal metabolic rate — 13%; 3,600,000 erythrocytes
January 11 to February 5	410	63	85	2,657	488	.....	1 2 3 4 5	42	Depressed, remorseful, confused, inactive; exquisite tender- ness of muscles of legs; high degree of muscular weak- ness; patellar reflexes active; blood pressure 130/85; pulse rate 80; heart sounds stronger; vasomotor hypotonia; basal metabolic rate — 25%; 3,600,000 erythrocytes
February 6 to March 25	398	63	85	2,609	409	3,000 7,500	1 2 3 4 5	785	By end of period sleeping well; fair appetite; cheerful; episodes characterized by fears, self accusations, agitation; general appearance improved; blood pressure 160/90 to 140/80; pulse rate 82; 4,220,000 erythrocytes
March 26 to May 31	355	62	87	2,451	485	7,500 6,000 2,000	5	.....	Further improvement; congenial, cooperative, industrious; stability of emotions; sleeps soundly; engaged in housework and choir; blood pressure 124/88; pulse rate 82; basal metabolic rate — 16%; 4,300,000 erythrocytes

\* The following dietary supplements (other than thiamine hydrochloride and the basal supplements) were given for study of the anemia associated with restriction of thiamine: (1) pyridoxine from Nov. 23, 1940 to March 25, 1941, with initial doses of 50 mg. daily; (2) riboflavin from Dec. 3, 1940 to March 25, 1941, with initial doses of 100 mg. daily; (3) nicotinic acid from Dec. 3, 1940 to March 25, 1941, with initial doses of 100 mg. daily; (4) calcium pantothenate from Dec. 24, 1940 to March 25, 1941, with initial doses of 1.0 Gm. daily.

† The clinical notes apply to the condition of the subject at the end of the period to which they are appended.

uncooperative and, without knowing why, fearful that some misfortune awaited them. Two became agitated, felt that life no longer was worth living and threatened suicide. All became inefficient in their work. In part this could be attributed to weakness, in part to inability to concentrate, confusion of thoughts and uncertainty of memory, which required repeated consultation of spoken or written instructions. All subjects lost manual dexterity; their hands and feet frequently felt numb; they injured themselves and broke equipment. Those engaged in sewing were inaccurate and frequently dropped their needles. Those assisting in the kitchen and laboratory with dishwashing broke the crockery.

It should be emphasized repeatedly that these abnormalities of behavior and efficiency had not been present during the period of preliminary observation, that they developed only after several weeks of restriction of thiamine and that they disappeared during a subsequent period in which the administration of thiamine, without the knowledge of the subjects, was the only modification of the experimental regimen.

Many other complaints were voiced, such as headache, backache, unusually painful menstrual periods, sleeplessness, tenseness, formication, inability to tolerate painful stimuli and sensitivity to noises. The significance of these subjective complaints is increased by the fact that the subjects were selected because they previously had not been complainers.

In this study of moderate restriction of thiamine the manifestations of deficiency were in many respects similar to those encountered in our earlier investigation of more severe restriction. In other respects they differed. Tolerance to exercise was affected less severely, and 5 subjects were able to do some work throughout the period of study. The exertion, however, was neither vigorous nor sustained. Finally, vigorous exertion became impossible. In general, manifestations of deficiency became progressively more severe. However, from week to week symptoms, signs and evidence of metabolic defects waxed and waned. Activity invariably would be reduced when weakness or nausea was experienced, and such periods of rest seemed to exert a recuperative effect, being followed by periods of relative remission of signs and symptoms. However, the interval between remission and exacerbation of the manifestations of deficiency became progressively shorter.

Impairment of gastrointestinal motility could not be demonstrated by serial roentgen examination of the subjects in this study, although anorexia with episodes of nausea and vomiting was observed in all cases and epigastric distress after meals was a frequent development. Also, constipation was the rule; diarrhea was unusual.

Abnormally elevated values for sugar in blood drawn while the subject was in the fasting state and high blood sugar time curves were frequently encountered when these examinations were made in periods of exacerbation of the symptoms of deficiency. The concentration of pyruvic

acid in the blood with the subject in the basal state sometimes was elevated, but not to the degree encountered in earlier studies in which the diet had been limited more rigidly in the matter of content of thiamine. The concentration of pyruvic acid in the blood after the intravenous injection of solution of dextrose was abnormally high in several subjects. Bueding and his co-workers<sup>12</sup> recently reported elevated values for pyruvic acid in the blood after the oral administration of dextrose to subjects with vitamin B<sub>1</sub> deficiency. We administered the solution of dextrose by vein because if the solution had been given by mouth, it would frequently have been vomited, and because the rate of absorption of the dextrose ingested orally could not be controlled.

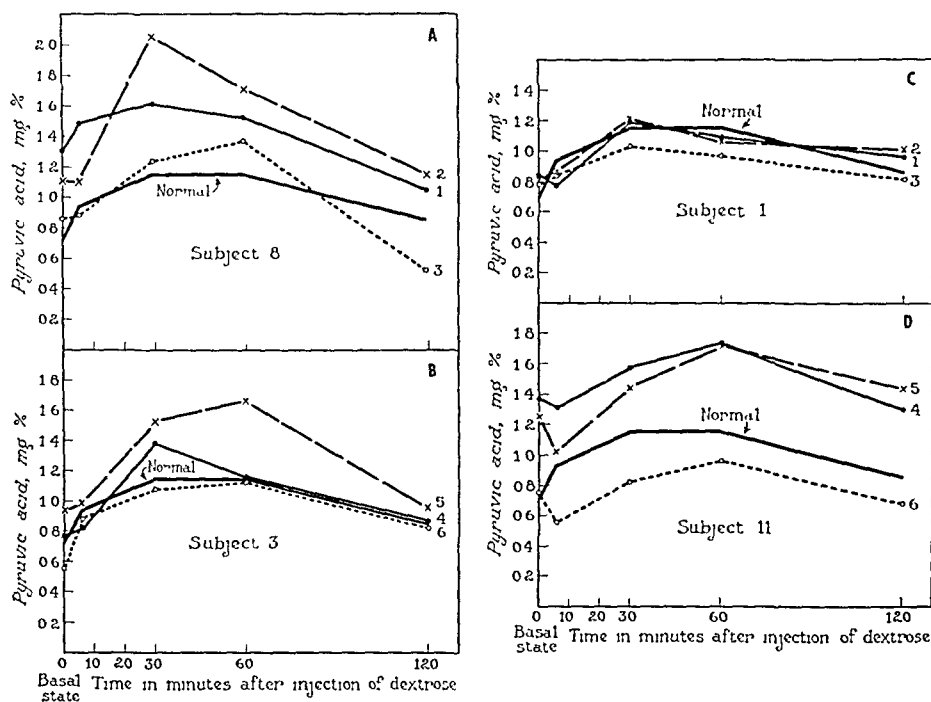


Figure 1

(See legend on opposite page)

Representative data concerning the concentration of pyruvate in the blood at various stages of deficiency are presented (fig. 1). Further study of this procedure as a test of thiamine subnutrition is in progress. Subject 1 (fig. 1 C) was much less severely affected by restriction of thiamine than the other subjects; she was continuously engaged in ward housekeeping and remained fairly efficient throughout the period (131 days) of low intake of thiamine. The blood pyruvic acid curve of this subject was not abnormal at any time, as compared with that of subjects in the control series.

12. Bueding, E.; Stein, M. H., and Wortis, H.: Blood Pyruvic Time Curves Following Glucose Ingestion in Normal and Thiamine-Deficient Subjects, *J. Biol. Chem.* **140**:697-703 (Sept.) 1941.

Abnormal electrocardiograms of the type previously reported<sup>1</sup> were detected in only 3 cases. Representative electrocardiograms are illustrated (fig. 2). Low blood pressure (85 to 100 systolic and 50 to 60 diastolic, expressed in millimeters of mercury) and vasomotor instability were observed in all cases. Blood pressure decreased sharply, and frequently there were pallor, giddiness and swaying when the subject assumed the erect posture. At rest the pulse rates were slow (55 to 60 per minute), but rapid pulse rates followed moderate exertion. Marked sinus arrhythmia developed in all subjects, and in 3 cases premature beats of auricular or nodal origin were detected by electrocardiographic examination. These 3 subjects periodically complained of palpitation and precordial distress. Other subjects also complained of precordial distress on exertion as well as of palpitation—often this awakened them from their sleep at night, causing anxiety on the score of "heart trouble." Vasomotor hypotonia associated with the peripheral neuropathy of thiamine deficiency was recently reported by Wilkins and Kolb.<sup>13</sup> De Soldati<sup>14</sup> reviewed the literature on circulatory disturbances in thiamine deficiency and commented on his observation of low blood pressure

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13. Wilkins, R. W., and Kolb, L. C.: Vasomotor Disturbances in Peripheral Neuritis, *Am. J. M. Sc.* **202**:216-221 (Aug.) 1941.

14. de Soldati, L.: Los trastornos circulatorios de la avitaminosis B<sub>1</sub>, Buenos Aires, El Ateneo, 1940.

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#### EXPLANATION OF FIGURE 1

Time curves of concentration of pyruvate in the blood following injection of a solution of dextrose (0.4 Gm. per kilogram of body weight given intravenously in three minutes). *Normal* indicates the composite curve of 10 subjects whose intakes of thiamine were known to have been adequate. *A*, (1) Dec. 31, 1940; thiamine had been restricted for 159 days (July 25 to December 31). (2) Jan. 23, 1941; thiamine had been restricted for 169 days (July 25, 1940 to Jan. 11, 1941), and 58 mg. of thiamine hydrochloride had been given in the 13 days (January 11 to 23) prior to the test. (3) May 8, 1941; the intake of thiamine had been adequate in the 117 days (January 11 to May 8) prior to the test. *B*, (4) Nov. 18, 1940; thiamine had been restricted for 116 days. (5) Dec. 12, 1940; thiamine had been restricted for 131 days (July 25 to December 4), and 22 mg. of thiamine hydrochloride had been given in the 7 days (December 4 to 12) prior to the test. (6) May 20, 1941; the intake of thiamine had been adequate for 81 days (March 1 to May 20) prior to the test. *C*, (1) Oct. 7, 1940; the intake of thiamine had been restricted for 74 days (July 25 to October 7). (2) Nov. 14, 1940; the intake of thiamine had been restricted for 112 days. (3) Dec. 18, 1940; the intake of thiamine had been restricted for 132 days (July 25 to December 4), and 40 mg. of thiamine hydrochloride had been given in the 14 days (December 4 to 18) prior to the test. *D*, (4) Sept. 12, 1940; thiamine had been restricted for 49 days. (5) Sept. 30, 1940; thiamine had been restricted for 67 days. (6) Nov. 1, 1940; thiamine had been restricted for 89 days (July 25 to October 22), and 56 mg. of thiamine hydrochloride had been given in the 12 days (October 22 to November 1) prior to the test.

in laboratory animals deprived of thiamine. Weiss<sup>15</sup> has reviewed his studies on cardiovascular abnormalities associated with thiamine deficiency. Elsom and co-workers<sup>16</sup> demonstrated that deficiency of thiamine was the etiologic factor in cardiovascular abnormalities which they observed in subjects with induced deficiency of the vitamin B complex.

Anemia, not detected in the earlier experiments, in which loss of weight had occurred, was observed in 5 subjects. It was of considerable

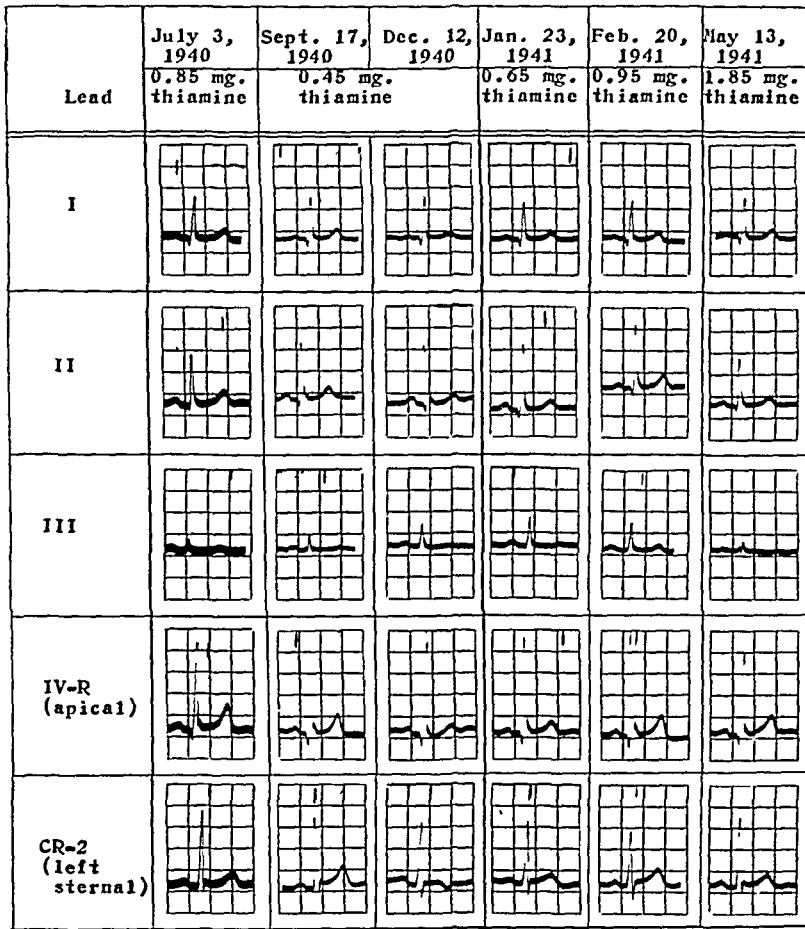


Fig. 2.—Typical electrocardiograms, made during the period of restriction of thiamine (July 25, 1940 to Jan. 13, 1941) and during subsequent periods (January 14 to May 30) in which the diet was supplemented with thiamine hydrochloride in increasing amounts.

degree (3,000,000 to 3,500,000 erythrocytes per cubic millimeter of blood) and was hyperchromic and macrocytic in type. In 3 cases it

15. Weiss, S.: Occidental Beriberi with Cardiovascular Manifestations: Its Relation to Thiamin Deficiency, *J. A. M. A.* **115**:832-839 (Sept. 7) 1940.

16. Elsom, K. O.; Lewy, F. H., and Heublein, G. W.: Clinical Studies of Experimental Human Vitamin B Complex Deficiency, *Am. J. M. Sc.* **200**:757-764 (Dec.) 1940.

was associated with the development of histamine-fast gastric achlorhydria. Bone marrow, obtained by puncture of the sternum, was in a hypoplastic state. The platelet count was not decreased; bleeding and clotting times were not prolonged, and there was normal retraction of the clot. Elsom and Sample<sup>17</sup> called attention to macrocytic anemia in states of spontaneous deficiency of the vitamin B complex in pregnant women, as well as in subjects with induced deficiency of the vitamin B complex.<sup>16</sup>

A decrease of the concentration of serum proteins was observed in 8 cases, and in 5 of them values for serum protein ranged from 4.9 to 5.7 Gm. per hundred cubic centimeters of serum. In general, when hypoproteinemia developed, anemia also occurred. A slight, pitting edema was observed in 1 case (subject 9).

Basal metabolic rates were irregularly lowered by 10 to 33 points. This depression of basal metabolic rate occurred even in the absence of anemia or significant change of weight. In 1 case (subject 10) in which the basal metabolic rate was — 17 per cent at the beginning of the study, the rate decreased to — 25 per cent, a decrease of only 8 points. In another case (subject 11) in which the basal metabolic rate was + 20 per cent (postoperative recurrent thyrotoxicosis of mild degree), the rate decreased to — 3 per cent, a decrease of 23 points. Intolerance to cold was a frequent complaint during the period of restriction of thiamine. An observation which may be significant was the instability of the basal metabolic rate. Rates varied greatly from week to week, even though the results of two tests made on each test day were in close agreement. The clinical picture was that of a patient with a variable but usually low basal metabolic rate associated with little or no change in weight, together with bradycardia, fatigue and numerous somatic symptoms. Signs and symptoms encountered among patients presenting different levels of basal metabolism were recently reviewed by Short<sup>18</sup> in an analysis of 1,000 cases.

The metabolic rates increased slowly when thiamine was again provided, but in 4 cases (subjects 1, 2, 4 and 9) the rates that had obtained during the period of preliminary observation were not regained before the end of the period of observation.

*Observations in the Period in Which the Diet Deficient in Thiamine Was Supplemented with Thiamine Hydrochloride.*—The period of restricted intake of thiamine was terminated for 8 subjects by the subcutaneous injection of 1.0 mg. of thiamine hydrochloride, followed by administration of 3.0 mg. of the vitamin daily for 7 days and thereafter

17. Elsom, K. O., and Sample, A. B.: Macrocytic Anemia in Pregnant Women with Vitamin B Deficiency, *J. Clin. Investigation* **16**:463-474 (May) 1937.

18. Short, J. J.: Incidence of Certain Signs and Symptoms at Various Levels of Basal and Total Resting Metabolism: Analysis of One Thousand Cases, *Am. J. M. Sc.* **201**:824-830 (June) 1941.

of 7.5 mg. daily. With the exception of the initial subcutaneous injection of 1 mg., the thiamine hydrochloride was administered orally in divided doses. In the period of restriction the subjects had been accustomed to receiving subcutaneous injections of physiologic solution of sodium chloride and to taking doses of a 2 per cent solution of acetic acid and capsules containing dextrose. The addition of the vitamin to these preparations was accomplished without their knowledge. Analysis of the urine for thiamine during the period in which the deficient diet was supplemented with thiamine hydrochloride provided evidence that the vitamin was being absorbed.

Physical and mental efficiency and sense of well-being gradually improved when, without change of diet or environment, thiamine was provided. However, in contrast to the observation made in our earlier studies of severe restriction of thiamine, in which prompt relief of the signs and symptoms of deficiency disease followed the administration of thiamine, fatigue, anorexia, dyspnea, tachycardia on moderate exertion and bradycardia at rest persisted for a longer time than in the earlier study.

The abnormal electrocardiographic patterns which were observed in 3 cases disappeared gradually; abnormal blood sugar time curves and concentrations of pyruvic acid returned to normal slowly, and the return to previous levels of the lowered basal metabolic rates was delayed.

This slow disappearance of signs and symptoms on treatment with thiamine of subjects submitted to prolonged, moderate restriction of thiamine provides a possible explanation for the frequent clinical observation that persons who have subsisted on poor diets, who excrete little thiamine in the urine and in whom deficiencies of other nutritional factors have been corrected, nevertheless have not been strikingly benefited by intensive treatment with thiamine for short periods.

*Requirement of Thiamine.*—In view of the possible influence of stored thiamine on the requirements of thiamine it appeared important to contrast data concerning subjects with initially "good" stores of thiamine with data concerning others known to have depleted, or "poor," stores of this vitamin in determinations of thiamine requirements. Therefore, 3 subjects (1, 2 and 3) subsisting on the standard diet were given 7.5 mg. of thiamine hydrochloride daily from Dec. 4, 1940 to Jan. 9, 1941 (37 days). These subjects thus had the opportunity to accumulate stores of thiamine and hence of cocarboxylase. Three others (subjects 4, 5 and 6) had been maintained for 169 days on the standard diet, which contained less than 0.45 mg. of thiamine daily. Their stores of the vitamin and hence of cocarboxylase undoubtedly were depleted.

On Jan. 10, 1941 and thereafter until May 31, 1941 the intake of thiamine of these 6 subjects was made identical. All received the standard diet and progressively increasing amounts of thiamine hydro-

chloride administered orally in solution. The average amounts of thiamine excreted at the increasing levels of intake are presented in table 7. The clinical courses of 2 of these subjects are shown in tables 3 and 4.

The average amounts of thiamine excreted in the urine of the subjects with good stores and those who had depleted stores soon became essentially identical.<sup>19</sup> In all subjects the first significant increase in excretion occurred when later the intake of thiamine was increased from 0.4 to 0.5 mg. per thousand calories of food. The criterion of excretion thus indicated that 0.4 mg. per thousand calories was what may be called a "minimal" requirement for these subjects. However, an intake of less than 0.5 to 0.6 mg. of thiamine for each 1,000 calories did not suffice to prevent some degree of fatigue, irritability, poor appetite, insomnia, sore-

TABLE 7.—Average Excretion of Thiamine During the Study of Thiamine Requirements\*

Intake of Thiamine		Excretion of Thiamine, 24 Hours			
		No Test Dose		"Test Dose" of Thiamine †	
		"Good" Stores	"Poor" Stores	"Good" Stores	"Poor" Stores
Mg.	Days				
7,500	37	3,960	.....	.....	.....
400	5	410	.....	510	.....
	132	.....	34	.....	153
600	22	127	58	325	224
800	22	130	105	335	312
1,000	20	214	181	399	383
1,200	16	265	210	554	454
1,400	14	397	381	632	592
1,600	14	598	510	938	879
1,800	13	651	590	1,090	902
2,000	14	823	709	1,129	1,066

\* Subjects with "good" stores had received 7.5 mg. of thiamine hydrochloride daily for 37 days prior to the study of requirements; those with "poor" stores, less than 0.45 mg. daily for 132 days prior to the study of requirements.

† One milligram of thiamine hydrochloride injected intramuscularly.

ness of muscles, decreased activity and a general feeling of "poor health," and on the basis of this information the desirable minimal level of intake of thiamine could be placed at 0.5 or 0.6 mg. per thousand calories. Under the conditions of this experiment, benefit was not observed to have been derived in any case from amounts of thiamine greater than 1.0 mg. for each 1,000 calories of the diet.

We previously demonstrated the fact that physically normal women lost weight but maintained themselves for 3 to 6 months on a daily intake of 0.07 mg. of thiamine for each 1,000 calories of a mixed diet. In the present study physically normal women maintained their weight for 169

19. Excretion of thiamine by individual subjects, together with a study of excretion after the injection of test doses of thiamine hydrochloride, are contained in a separate report (Mason, H. L., and Williams, R. D.: The Urinary Excretion of Thiamine as an Index of the Nutritional Level: Assessment of the Value of a Test Dose, *J. Clin. Investigation* **21**:247-255 [March] 1942).



days on a daily intake of 0.22 mg. of thiamine per thousand calories of a mixed diet. They did not maintain good health. On the contrary, they all suffered impairment of physical and mental efficiency, with manifest evidence of biochemical abnormalities. They lived on a plane of vitality lowered by a deficiency of thiamine, a plane which could be raised again only by the administration of thiamine.

Thus, our data indicate that the "minimal" intake of thiamine requisite to the maintenance of health, when the diet is of conventional composition with respect to proportions of carbohydrate and fat, must be more than 0.22 mg. for each 1,000 calories and that from 0.5 to 0.6 mg. for each 1,000 calories is necessary for the maintenance of efficiency.

#### SUMMARY

As previously reported, severe restriction of thiamine was found to be associated with states of inactivity, apathy, serious derangement of metabolic processes, loss of weight and, finally, prostration.

In the present study moderate, prolonged restriction of this vitamin, but not of food calories, was associated with states of emotional instability reflected by irritability and moodiness, quarrelsomeness, lack of cooperation, vague fears progressing to agitation, mental depression, variable restriction of activity and numerous somatic symptoms. Detectable metabolic disturbances, occurring irregularly, were of variable degree of severity and were reflected in disturbance of function of various tissues of the body.

In all cases of induced deficiency of thiamine, mental and physical inefficiency preceded by weeks or months other more objective manifestations of deficiency of thiamine.

In previously reported studies subjects maintained themselves as long as 147 days on intakes of thiamine not greater than 0.07 mg. for each 1,000 calories of the diet, but they lost weight and strength. In the present study subjects maintained their weight on an intake of 0.22 mg. for each 1,000 calories, but their physical and mental efficiency and their sense of well-being was greatly improved when 0.5 mg. of thiamine hydrochloride was provided with this number of calories. Thus, the data indicate that for the subjects of this study the "minimal" daily requirement of thiamine was between 0.22 and 0.50 mg. for each 1,000 calories of a diet providing carbohydrates and fat in conventional proportions. The data indicate, however, that the "optimal" intake was not less than 0.5 mg. or more than 1.0 mg. for each 1,000 calories of such a diet.

Individual variations dependent on differences in the rate of metabolic exchanges of energy or material, as well as on environmental factors, activity, diet and intestinal absorption, must receive consideration when the requirement of thiamine of the individual person is judged.

# DUPLICATE MEASUREMENTS OF CIRCULATION TIME MADE WITH THE ALPHA LOBELINE METHOD

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AND

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Last year one of us (K. B.)<sup>1</sup> reported his experience with alpha lobeline hydrochloride as an agent for measuring the velocity of blood flow, a method originally proposed by Teplov and Sor.<sup>2</sup> Its advantages and disadvantages were commented on, and the conclusion was reached that it was a practical method for testing "circulation time." We then planned to employ the test in evaluating the progress of patients who were under treatment for heart failure. The day to day variations observed in the same patient were considerable, and it occurred to us that factors other than changes in the degree of heart failure might be operative. To investigate this problem, a series of duplicate measurements was performed, the results of which are presented here.

## DESCRIPTION OF TEST

The technic of the test has been previously outlined in detail<sup>1</sup>; a brief description will suffice here. Three to 5 mg. of alpha lobeline hydrochloride (0.3 to 0.5 cc. of the 1 per cent solution<sup>3</sup>) is rapidly injected into an antecubital vein. Several seconds later the patient coughs. The interval from the beginning of the injection to the onset of coughing represents the "circulation time" for that patient. If cough fails to appear, the test is repeated with 7.5 to 10 mg. of the drug ten to fifteen minutes later.

## METHOD

One hundred patients were tested, 67 males and 33 females. They varied in age from 14 to 73 years, with an average age of 45 years. Thirty-nine patients were without evidence of heart disease; 61 were suffering from various forms of cardiac involvement. Of the latter group, 23 showed signs of congestive heart failure. The alpha lobeline test was performed twice on each patient. In 31

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From the Department of Cardiology, Sydenham Hospital.

1. Berliner, K.: Use of Alpha Lobeline for Measurement of Velocity of Blood Flow, *Arch. Int. Med.* **65**:896 (May) 1940.

2. Teplov, I., and Sor, V. G.: Graphic Method for Determining the Velocity of Blood Circulation by Means of Lobeline, *Terap. ark.* (no. 2) **13**:57-80, 1935.

3. The ampules of alpha lobeline hydrochloride used in this study were supplied by the Sandoz Chemical Works, Inc., New York.

instances the interval between tests was fifteen to twenty minutes. In the remaining 69 the interval varied between twenty-five and sixty minutes (sixty minutes in 47 of these). Care was taken to make the conditions of the second test identical with those of the first as regards the dose, the gage of the needle, the speed of injection and the position of the patient. The patients were at rest during the interim. All tests were performed in the morning, between breakfast and lunch.

### RESULTS

The results of the first and the second test were identical in only 3 cases. In most of the other 97 cases the difference in results between the first and the second test was considerable. In 12 cases the second

TABLE 1.—*Comparison of the Results of the First and the Second Test in One Hundred Duplicate Measurements of Circulation Time*

Number of Duplicate Measurements	Comment
44	Results of first test higher
41	Results of first test lower
3	Results identical
12	Second test a failure

TABLE 2.—*Differences in the Results of the First and the Second Test, Expressed in Percentages of the First Result, in One Hundred Duplicate Measurements of Circulation Time*

Number of Duplicate Measurements	Difference
3	None
20	Less than 10 per cent
22	10 to 19 per cent
30	20 to 49 per cent
9	50 to 99 per cent
4	100 to 199 per cent
12	Second test a failure

injection of alpha lobeline failed altogether to produce cough. Such failure of the second test occurred with about the same frequency in patients without heart disease as in patients with heart disease, regardless of the presence of congestive failure. Table 1 summarizes the results and also shows that in 44 cases the result of the second test was higher than that of the first, whereas in 41 cases the result of the second test was lower. Table 2 illustrates the degree of difference in results, expressed in percentages. This was less than 10 per cent in only 20 cases but as high as 50 to 199 per cent in 12 cases. In 52 cases, the largest group, differences in results varied from 10 to 49 per cent.

Such factors as the age of the patient and the amount of alpha lobeline used did not affect the difference between the results of the first

and the second test, nor did it matter whether the interval between the first and the second test was fifteen minutes or one hour. On the other hand, it was of significance whether the patient had heart disease, and it was of still greater significance whether congestive heart failure was present (table 3). For patients without heart disease, circulation times ranged from 4.9 to 16.5 seconds, with an average of 9.5 seconds. The average difference between the first and the second test in this group was 20 per cent. For patients with heart disease without congestive failure, circulation times ranged from 5.0 to 34.5 seconds, with an average of 11.5 seconds, and the average difference between the results of the first and the second test was 34 per cent. For persons with heart disease and with evidence of congestive failure, we observed circulation times ranging from 7.3 to 31.6 seconds, with an average of 17 seconds,

TABLE 3.—*Relation of the Results of Duplicate Measurement of Circulation Time to the Cardiac Status of the Subjects*

Cardiac Status	No Cardiac Disease	Cardiac Disease Without Congestive Failure	Cardiac Disease With Congestive Failure
Number of subjects.....	39	37	24
Range of circulation time.....	4.9 to 16.5 sec.	5.0 to 34.5 sec.	7.3 to 31.6 sec.
Average circulation time.....	9.5 sec.	11.5 sec.	17.0 sec.
Results of first and second test identical	2	1	0
Second test a failure.....	3	3	6
Range of differences between results of first and second test	3.2 to 50.9% (0.3 to 8.5 sec.)	2.6 to 109.0% (0.2 to 28.6 sec.)	7.1 to 151.9% (0.6 to 20.0 sec.)
Average difference between results of first and second test	20%	34%	49%

and in this group the average difference between the results of the two tests was highest (49 per cent).

#### COMMENT

For a number of reasons duplicate measurements of circulation time may give varying results, no matter what method is used. It should be remembered that the results of most measurements of circulation time represent velocity of blood flow plus "reaction time."<sup>4</sup> Velocity of blood flow is affected by numerous factors other than congestive heart failure, e. g., exercise, excitement, digestion, fever, basal metabolic rate, hemoglobin content, volume of circulating blood, vitamin B deficiency and pathologic states of the vascular system.

4. Spier, L. C.; Wright, I. S., and Saylor, L.: A New Method for Determining the Circulation Time Throughout the Vascular System, *Am. Heart J.* **12**:511, 1936.

Reaction time, on the other hand, is also affected by several factors, the importance of which varies with the method used. These factors include the patient's intelligence and willingness to cooperate (in the subjective methods) and the physiologic state of the patient's nervous system. In duplicate measurements, reaction time is probably more variable than velocity of blood flow. This seems to apply particularly to duplicate measurements made with lobeline; in the present study, the intervals between tests were so short and the differences found often so great that the possibility of change in the actual velocity of blood flow was remote.

Additional factors also may play a part. To begin with, certain technical points should be considered, e.g., slight variations in the speed of injection. These probably occurred in our series, but they cannot account for the wide differences noted, since the small amount of material used permitted great rapidity of injection. (This factor may play a greater part in methods which require larger amounts of material.) Since the same vein could not always be used for both injections, differences in caliber of the veins may also have played a minor role. Next, the possibility of variations in strength of the drug should be borne in mind. Stanojevic and Djordjevitch<sup>5</sup> reported finding such variations in their supply of alpha lobeline. In our series, material for duplicate measurements was often taken from different ampules, but these always belonged to the same batch, and we have no reason to suspect significant variations in strength.

While the patients studied were at rest in bed, they were not in basal condition. This circumstance may account, in part, for the variations observed. Nevertheless, we studied the patients in this manner because we were interested in the usefulness of the alpha lobeline test under ordinary clinical conditions.

In addition, the factors of cumulative effect and drug tolerance were considered. These factors seemed unimportant, because the second result was higher than the first just as frequently as it was lower. If cumulation had accounted for the variation in results, the second result should always have been lower. Conversely, if tolerance had developed, the second result should have been uniformly higher.

The exact mechanism of the effect of alpha lobeline is not yet fully understood. It is, however, definitely known that stimulation of the respiratory center occurs, probably by way of a reflex from the carotid sinus.<sup>6</sup> It is possible that variations in the irritability of the respiratory

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5. Stanojevic, L., and Djordjevitch, B.: Sur la détermination du temps de circulation par la lobéline, *Compt. rend. Soc. de biol.* **127**:1362, 1938.

6. Heymans, C.; Bouckaert, J. J., and Dautrebande, L.: Sinus carotidiens et actions stimulantes respiratoires de la nicotine et de la lobéline, *Compt. rend. Soc. de biol.* **106**:469, 1931; Sinus carotidiens et sensibilité réflexogène respiratoire aux agents chimiques, *ibid.* **109**:56, 1932.

center of the reflex arc itself may occur which are independent of the state of the circulation. Such variations may account for the absolute failure of the second test in 12 instances, including some patients with and some without heart disease.

It is evident, therefore, that many factors may affect the results of duplicate measurements; yet we are unable to give an adequate explanation for the marked variations observed.

We reviewed the literature in order to learn whether other investigators had obtained more uniform results with duplicate measurements of alpha lobeline circulation time and whether duplicate measurements made with other methods had given more consistent results.

We found only two reports of duplicate measurements made with alpha lobeline, both dealing with small series. Stanojevic and Djordjevitch<sup>5</sup> measured circulation time once a day in 20 cases and observed variations of three to four seconds (six seconds in 1 instance) in patients without cardiac disease. While the interval between their tests was much longer, the percentage variations were comparable to those reported here. Mosco<sup>7</sup> made duplicate measurements in 16 cases, using the same amount of alpha lobeline for both tests on only 1 subject and different amounts for the others. The second test was performed less than five minutes after the first. The results of his duplicate tests were practically identical. The same author reported 10 duplicate measurements with an interval of one to ten days; the results of these were also practically identical. We cannot explain this striking agreement in results, which is in marked contrast to our own experience.

The literature contains several reports of duplicate measurements by other methods. Blumgart and Weiss,<sup>8</sup> employing the radium-active deposit method, reported 14 duplicate tests of arm to arm circulation time. Only 4 of these were performed on the same day. Of the 4, 3 showed remarkable agreement in the results, while the fourth showed a variation of 28 per cent. These authors<sup>9</sup> also reported 8 duplicate measurements of the arm to arm circulation time determined by the same method. Five of these were performed on the same day; 3 were in fairly close agreement, whereas 2 showed variations of about 20 per cent. Weiss, Robb and Blumgart,<sup>10</sup> using the histamine method, reported 12 duplicate measurements. The interval between tests varied from three

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7. Mosco, D.: La velocità di circolo in riposo e subito dopo un esercizio fisico in una centuria d'individui sani, *Endocrinol. e pat. costit.* **15**:3, 1940.

8. Blumgart, H. L., and Weiss, S.: Studies on the Velocity of Blood Flow: II. The Velocity of Blood Flow in Normal Resting Individuals, *J. Clin. Investigation* **4**:23, 1927.

9. Blumgart, H. L., and Weiss, S.: Studies on the Velocity of Blood Flow: VII. Pulmonary Circulation Time in Normal Resting Individuals, *J. Clin. Investigation* **4**:399, 1927.

10. Weiss, S.; Robb, G. P., and Blumgart, H. L.: The Velocity of Blood Flow in Health and Disease, *Am. Heart J.* **4**:670, 1929.

to thirteen minutes. The results agreed within 10 per cent or less in 10 cases, while in 2 cases the differences were 14 and 21 per cent, respectively.

We found four reports of duplicate measurements with other agents. Tarr, Oppenheimer and Sager<sup>11</sup> used sodium dehydrocholate and obtained "remarkable agreement" in duplicate tests on normal subjects, with differences not exceeding three seconds. In patients with prolonged circulation time, however, fluctuations up to eight seconds occurred. Details of the duplicate tests were not given. Gargill,<sup>12</sup> employing the same method and leaving the needle in situ, made triplicate tests on over 150 subjects. He found that the "three measurements usually checked within one second or a fraction thereof." Goldberg,<sup>13</sup> employing calcium gluconate as an agent, repeated the test after one or two minutes, without removing the needle from the vein and found that "the second reading usually checks closely with the first." These various reports show a greater uniformity of results than was obtained by us with alpha lobeline. On the other hand, Esser and Berliner,<sup>14</sup> who made duplicate measurements with the saccharin method,<sup>15</sup> found considerable differences between the results of the first and the second test. Their tests, carried out under conditions similar to those of the present study, had an interval of sixty minutes. For 21 subjects without cardiac disease, the average difference between the results of first and those of the second test was 21.8 per cent, about the same as the difference reported here (20 per cent).

On one important point our own observations are in accord with those of various other investigators<sup>16</sup> using different methods; namely, duplicate measurements of circulation time show the greatest variations in patients suffering from congestive heart failure. Since our results were expressed in terms of percentage difference, they clearly indicate that the variations found in this group are disproportionately greater than those found in the other two groups. The observation is of practical significance because tests of circulation time are most frequently

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11. Tarr, L.; Oppenheimer, B. S., and Sager, R. V.: The Circulation Time in Various Clinical Conditions Determined by the Use of Sodium Dehydrocholate, *Am. Heart J.* **8**:766, 1933.

12. Gargill, S. L.: The Use of Sodium Dehydrocholate as a Clinical Test of the Velocity of Blood Flow, *New England J. Med.* **209**:1089, 1933.

13. Goldberg, S. J.: The Use of Calcium Gluconate as a Circulation Time Test, *Am. J. M. Sc.* **192**:36, 1936.

14. Esser, K., and Berliner, K.: Duplicate Measurements of Circulation Time Made with the Saccharin Method, to be published.

15. Fishberg, A. M.; Hitzig, W. H., and King, F. H.: Measurement of Circulation Time with Saccharin, *Proc. Soc. Exper. Biol. & Med.* **30**:651, 1933.

16. Weiss, Robb and Blumgart.<sup>10</sup> Tarr, Oppenheimer and Sager.<sup>11</sup> Esser and Berliner.<sup>14</sup>

performed on patients suffering from heart failure. It would appear, therefore, that tests of circulation time in general and the alpha lobeline test in particular should not be relied on to evaluate the progress of a patient in congestive heart failure unless the changes shown by these tests are marked.

In the previous report it was concluded that the alpha lobeline test is a practical method for determining the velocity of blood flow. The results of the present study indicate definite limitations of its usefulness.

#### SUMMARY

One hundred duplicate measurements of circulation time were made, with alpha lobeline hydrochloride used as an agent. The interval between tests varied from fifteen to sixty minutes.

Considerable differences in the results of the duplicate tests were observed in many instances. In only 3 cases were identical results obtained. In 85 cases the differences varied from 3 to 199 per cent, with an average variation of 29 per cent. The result of the second test was higher than that of the first just as frequently as it was lower. In 12 cases the second injection failed altogether to produce cough.

The factors which may have been responsible for the variations in results are discussed.

Differences in the results of duplicate tests were greatest in patients suffering from congestive heart failure. Other investigators using different methods reported the same observation. Tests of circulation time in general and the alpha lobeline test in particular should not be relied on to evaluate the progress of a patient with congestive heart failure unless the changes shown by these tests are marked.



# NEOARSPHENAMINE THERAPY OF BACTERIAL INFECTIONS

WITH A METHOD OF ADMINISTRATION TO MAINTAIN UNIFORM BLOOD LEVELS FOR THE TREATMENT OF SERIOUS STAPHYLOCOCCIC INFECTIONS AND SUBACUTE BACTERIAL ENDOCARDITIS

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Neoarsphenamine has been widely used in the therapy of syphilis since the synthesis of the drug by Ehrlich, but it has received relatively little attention as a chemotherapeutic agent against other bacterial infections. Reports by E. LeCocq<sup>1</sup> and J. LeCocq<sup>2</sup> of its effectiveness in the treatment of serious staphylococcic infections led to experimental<sup>3</sup> and clinical<sup>4</sup> confirmation of its effectiveness against staphylococci. This paper summarizes results of studies in progress, details of which were presented in an exhibit at the 1941 session of the American Medical Association and will appear in subsequent publications. It is hoped that

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1. LeCocq, E.: The Use of Neosalvarsan in the Treatment of Acute Osteomyelitis and Blood Stream Infections Caused by the *Staphylococcus Aureus*, West. J. Surg. **44**:655-656 (Nov.) 1936.

2. LeCocq, J.: Personal communication to the author.

3. (a) Osgood, E. E.: Marrow Cultures, in A Symposium on the Blood and Blood-Forming Organs, Madison, Wis., University of Wisconsin Press, 1939, pp. 219-241; (b) Culture of Human Marrow: Studies of the Relative Effectiveness of Neoarsphenamine, Mapharsen, Sulfanilamide, Sulfapyridine, Sulfathiazole, and Sulfamethylthiazole on Infections with *Streptococcus Viridans* (Alpha Hemolytic *Streptococcus*), Am. J. M. Sc. **200**:596-603 (Nov.) 1940. (c) Osgood, E. E.; Joski, J., and Brownlee, I. E.: The Superiority of Neoarsphenamine and Sulfathiazole in the Therapy of *Staphylococcus Aureus* Infections in Marrow Cultures, Surg., Gynec. & Obst. **71**:445-450 (Oct.) 1940. (d) Osgood, E. E.: The Chemotherapy of Staphylococcic Infections, J. Pediat. **17**:740-746 (Dec.) 1940.

4. LeCocq,<sup>1</sup> Osgood.<sup>3d</sup>

this summary will stimulate further investigation of neoarsphenamine and related compounds as chemotherapeutic agents against bacterial infections.

In previous publications,<sup>3</sup> by use of the marrow culture technic, which permits controlled quantitative studies of the effectiveness of chemotherapeutic agents against bacterial infections in the presence of living human cells, it has been shown that neoarsphenamine is highly effective against staphylococci and certain groups of *Streptococcus viridans* (alpha streptococcus). The effective concentration has been shown to be 1:150,000, with an effective range from 1:100,000 (1.0 mg. per hundred cubic centimeters of culture medium) to 1:300,000 (0.3 mg. per hundred cubic centimeters of culture medium), or a range of 65 to 200 micrograms of arsenic per hundred cubic centimeters of culture medium. Lower concentrations were ineffective, and higher concentrations were toxic to the marrow cells (fig. 1) over a period

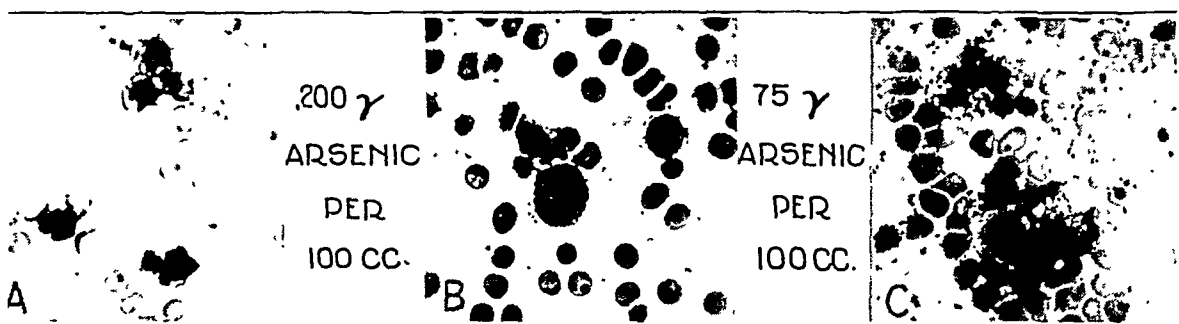


Fig. 1.—The comparative effectiveness and toxicity of different concentrations of neoarsphenamine. Those above 200 micrograms of arsenic per hundred cubic centimeters of culture medium damage marrow cells (*A*). Those between 75 and 200 micrograms of arsenic per hundred cubic centimeters of culture medium do not damage cells and are effective against bacteria (*B*). Those below 75 micrograms of arsenic per hundred cubic centimeters of culture medium are ineffective against bacteria (*C*).

of time. It has been further shown that neoarsphenamine has to be present in this concentration for an appreciable period, from forty-eight to seventy-two hours or longer, in order to insure maximum effect. As has been shown for the sulfanilamide group of drugs,<sup>5</sup> neoarsphenamine is less effective the larger the inoculum and is ineffective against large inoculums.

5. (a) Osgood, E. E.: Culture of Human Marrow: Studies on the Mode of Action of Sulfanilamide, *J. A. M. A.* **110**:349-356 (Jan. 29) 1938; (b) Culture of Human Marrow: A Comparative Study of the Effects of Sulfanilamide and Antipneumococcus Serum on the Course of Experimental Pneumococcic Infections, *Arch. Int. Med.* **62**:181-198 (Aug.) 1938. (c) Bullowa, J. G. M.; Osgood, E. E.; Bukantz, S. C., and Brownlee, I. E.: The Effect of Sulfapyridine Alone and with Serum on Pneumococcic Pneumonia and on Pneumococcus-Infected Marrow Cultures, *Am. J. M. Sc.* **199**:364-380 (March) 1940. (d) Osgood and others.<sup>3</sup>

COMPARATIVE EFFECTIVENESS OF NEOARSPHENAMINE, OTHER ARSENI-  
CALS AND DRUGS OF THE SULFANILAMIDE GROUP  
AGAINST VARIOUS BACTERIAL INFECTIONS

Since my previous publications alone, and with associates,<sup>5</sup> more than 100 marrow culture experiments of the type illustrated by tables

TABLE 1.—Comparative Effectiveness of Neoarsphenamine and Drugs of the Sulfanilamide Group in Sterilization of Marrow Cultures of *Neisseria Gonorrhoeae*

Note that the gonococcus grows well in marrow cultures and that five of the drugs, including neoarsphenamine, are superior to sulfanilamide and sulfanilamide E. O. S. (an addition compound of equimolar proportions of sulfanilamide, acetaldehyde and sodium bisulfite, having the formula  $H_2N=SO_2=C_6H_4=NH-\overset{\text{OH}}{\underset{|}{CH}}=SO_3Na$ ). The data in table 5 were com-  
piled from many experiments similar to those illustrated in tables 1 to 4 on different strains of each organism, in which the size of the initial inoculum varied widely. The gonococcus is much the most susceptible of the organisms studied, and an initial inoculum of 1,000,000 per cubic centimeter of culture medium was sterilized by sulfathiazole and sulfadiazine, which proved to be the most effective drugs. Note that neoarsphenamine can lead to sterility of gonococcal infections.

	Hours		
	0	23	48
Control. ....	640*	170,000,000*	95,000,000*
Neoarsphenamine, 0.005 mg. per cc. ....	640	0	0
Sulfanilamide, 0.05 mg. per cc. ....	640		105,000,000
Sulfanilamide, E. O. S., 0.05 mg. per cc. ...	640	60,800,000	77,500,000
Sulfathiazoline,† 0.05 mg. per cc. ....	640	0	0
Sulfapyridine, 0.05 mg. per cc. ....	640	0	0
Sulfadiazine, 0.05 mg. per cc. .	640	0	0
Sulfathiazole, 0.05 mg per cc. .	640	0	0

\* Colonies per cubic centimeter.  
† 2-sulfanilyl-3,5-dihydrothiazole.

TABLE 2.—Comparative Effectiveness of Neoarsphenamine and Drugs of the Sulfanilamide Group in Sterilization of Marrow Cultures of a Beta Hemolytic *Streptococcus*

Note that nearly all of the drugs studied are superior to sulfanilamide in their effect against the beta hemolytic streptococcus, even though sulfanilamide will readily sterilize small inoculums of less than 500 organisms per cubic centimeter of culture medium. Note also that neoarsphenamine was almost as effective as sulfathiazole against this organism and that sulfathiazoline (2-sulfanilyl 3,5-dihydrothiazole), sulfapyridine and sulfadiazine were intermediate in effectiveness. This table illustrated well the time that is necessary for the action of these drugs. Against some strains of the beta hemolytic streptococcus neoarsphenamine was superior to any of the drugs studied. The notation "acid" signifies that at some time the colony count was 100,000,000 or higher.

	Hours				
	0	18	42	66	72
Control. ....	3,400*	60,000,000*	Acid		
Sulfanilamide, 0.05 mg. per cc. .	3,400	170,000	32,000,000*	Acid	
Neoarsphenamine, 0.005 mg. per cc. .	3,400	690	0	0	0
Sulfathiazoline, 0.05 mg. per cc. ...	3,400	2,000	187	0	0
Sulfapyridine, 0.05 mg. per cc. .	3,400	1,550	155	0	0
Sulfadiazine, 0.02 mg. per cc. .	3,400	310,000	3,530,000	Acid	
Sulfadiazine, 0.05 mg. per cc. ...	3,400	13,000	100	1	0
Sulfathiazole, 0.02 mg. per cc. ..	3,400	325	0	0	0
Sulfathiazole, 0.05 mg. per cc. .	3,400	100	0	0	0

\* Colonies per cubic centimeter

1 to 4 have been performed. The results of these, which are summarized in table 5, indicate that neoarsphenamine is the most effective of any of the arsenicals studied and that it is capable of sterilizing mar-

row cultures inoculated with certain groups of *Str. viridans*, all staphylococci studied, some beta hemolytic streptococci belonging to Lancefield group A and gonococci. It was more effective than sulfanilamide against beta hemolytic streptococci and gonococci but not as effective

TABLE 3.—*Comparative Effectiveness of Arsenicals and Drugs of the Sulfanilamide Group in Sterilization of Marrow Cultures of Streptococcus Viridans*

This experiment on *Str. viridans* of group B shows that this strain responds well both to neoarsphenamine and to sulfathiazole, that arsenic trioxide is not nearly as effective as neoarsphenamine and that sodium formaldehyde sulfoxylate is ineffective in a concentration greater than that of the related group of neoarsphenamine when the concentration of neoarsphenamine is that used in this experiment. Similar experiments showed that mapharsen in a concentration one-tenth that of neoarsphenamine was almost ineffective against the alpha streptococcus as a rule.

	Hours				
	0	4	24	48	71
Control .....	240*	105*	730*	231,000*	241,000,000*
Neoarsphenamine, 0.0056 mg. per cc....	240	60	10	600	23
Arsenic trioxide, 0.0013 mg. per cc. ....	240	50	3,700	42,200,000	195,000,000
Sodium parantitrobenzoate, 0.15 mg. per cc. ....	240	70	3	0	0
Sulfathiazole, 0.1 mg. per cc. ....	240	0	0	0	0
Sodium formaldehyde sulfoxylate, 0.0025 mg. per cc. ....	240	100	1,700	1,500,000	229,000,000
Sodium formaldehyde sulfoxylate, 0.005 mg. per cc. ....	240	70	16,300	9,400,000	206,000,000

\* Colonies per cubic centimeter.

TABLE 4.—*Comparative Effectiveness of Neoarsphenamine and Drugs of the Sulfanilamide Group in the Sterilization of Marrow Cultures of Staphylococcus Aureus*

Note how much less susceptible to the action of the drugs is *Staph. aureus* than are the preceding organisms. An inoculum of 10 to 100 organisms per cubic centimeter of medium may be sterilized, however. Neoarsphenamine is much the most effective drug, with sulfathiazole next. Sulfadiazine in a concentration twice that of sulfathiazole is not nearly as effective, and sulfapyridine is only slightly effective. Sulfathiazoline (2-sulfanilyl-3,5-dihydrothiazole) and sulfanilamide are practically without effect on an inoculum of this size, although significant differences from the control are found in smaller inoculums. The notation "acid" means that the colony count at some time was as high as 400,000,000.

	Hours		
	0	16	22
Control .....	490*	500,000,000*	Acid
Neoarsphenamine, 0.005 mg. per cc. ....	490	83	170*
Sulfanilamide, 0.1 mg. per cc. ....	490	550,000,000	Acid
Sulfathiazoline, 0.1 mg. per cc. ....	490	410,000,000	Acid
Sulfapyridine, 0.1 mg. per cc. ....	490	70,000,000	230,000,000
Sulfadiazine, 0.2 mg. per cc. ....	490	3,900,000	16,300,000
Sulfathiazole, 0.1 mg. per cc. ....	490	30,000	16,000

\* Colonies per cubic centimeter.

as sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) and sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine) against these organisms. It was ineffective against the pneumococci studied. The other arsenicals were not nearly as effective as neoarsphenamine when used in concentrations differing from that of neoarsphenamine by the ratios of their clinical doses.

All of the twenty-five strains of *Str. viridans* so far investigated fall in one of three groups, as shown in table 5, which differ widely in their susceptibility to the action of neoarsphenamine and of sulfathiazole.

TABLE 5.—*Comparative Effectiveness of Chemotherapeutic Agents Against Bacteria*

The data in this table were compiled from many such experiments as those illustrated in tables 1 to 4. It must be remembered that the least effective drugs against the most susceptible organisms, which are *N. gonorrhoeae* and the beta hemolytic streptococcus, will be far more effective against these organisms than the most effective drug against less susceptible organisms, such as staphylococci. The organisms are arranged in order of decreasing susceptibility. *Escherichia coli*, *Eberthella typhosa* and *Salmonella schottmüller* are still less susceptible than staphylococci. Against these sulfathiazole was much the most effective drug. Against the pneumococci the concentration of sulfadiazine has to be about four times that of sulfathiazole to have equal effectiveness. When both were effective, the combination of neoarsphenamine and sulfathiazole was more effective than either alone. The combination of antiserum and the effective drug against the pneumococcus was more effective than either alone. The absolute effectiveness in terms of the concentration obtainable clinically will not necessarily be the only factor in deciding which is the best drug, since clinical toxicity and other factors must also be considered, as well as the data given here. Strain differences were observed among the other organisms but no such complete reversal of the order of effectiveness of the drugs as was observed among the three groups of alpha streptococci, which were not separable by bacteriologic methods.

Organism	Chemotherapeutic Agent		
	Most Effective	Less Effective	Least Effective
<i>Neisseria gonorrhoeae</i>	Sulfathiazole Sulfadiazine	Sulfapyridine Sulfathiazoline *	Neoarsphenamine Sulfanilamide Sulfanilamide E. O. S.†
Beta hemolytic streptococci	Sulfathiazole Neoarsphenamine	Sulfapyridine Sulfathiazoline Sulfadiazine	Sulfanilamide
Pneumococci	Sulfathiazole Sulfamethylthiazole ‡ Sulfapyridine	Sulfathiazoline Sulfadiazine	Sulfanilamide E. O. S. Sulfanilamide Sulfaphenylthiazole § Sodium sulfanilylsulfanilate Neoarsphenamine
<i>Streptococcus viridans</i>			
Group A	Neoarsphenamine	.....	Mapharsen Sulfathiazole Sulfamethylthiazole Sulfapyridine Sulfanilamide
Group B	Neoarsphenamine Sulfathiazole Sulfadiazine Sulfapyridine Sulfamethylthiazole Sodium paranitrobenzoate	Sulfanilamide Mapharsen Solarson	Arsenic trioxide Sodium cacodylate Sodium formaldehyde sulfoxylate
Group C	Sulfathiazole Sulfamethylthiazole Sulfapyridine Sulfadiazine	Sulfanilamide Sodium paranitrobenzoate	Neoarsphenamine
Staphylococci	Neoarsphenamine Sulfathiazole Sulfamethylthiazole	Sulfapyridine Sulfadiazine Sulfathiazoline	Sulfanilamide Sulfanilamide E. O. S. Sodium formaldehyde sulfoxylate Hydrogen peroxide

\* 2-sulfanilyl-3,5-dihydrothiazole.

† An addition compound of equimolar proportions of sulfanilamide, acetaldehyde and sodium bisulfite, having the formula  $N_2H=SO_2=C_6H_4=NH=CH=SO_3Na$ .

‡ 2-(paraaminobenzenesulfonamido)-4-methylthiazole.

§ 2-(paraaminobenzenesulfonamido)-4-phenylthiazole.

CH<sub>3</sub>

Organisms of group A respond to neoarsphenamine but not to the drugs of the sulfanilamide group; those of group B respond both to neoarsphenamine and to sulfathiazole and related compounds of the sulfanila-

mide group, and those of group C respond to sulfathiazole and sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) but not to neoarsphenamine. Bacteriologic and serologic studies<sup>6</sup> failed to reveal any clearcut criteria for separation of these three groups of alpha streptococci, although the organisms of group A are more difficult to grow on blood agar pour plates and colony counts are therefore difficult to obtain. The organisms of group A grow well in marrow cultures, however. The number of strains falling in groups A and B are about equal to the number of strains falling in group C. All of the strains of alpha streptococci, except two, fulfilled the criteria for *Streptococcus*

TABLE 6.—*Effects of Temperature Variations on the Action of Neoarsphenamine and Sulfathiazole on Staphylococcus Aureus*

Note that neoarsphenamine is more effective than sulfathiazole against *Staph. aureus* and that the effects of temperature on the action of the two drugs were similar, the counts not being significantly different from the counts of the control at icebox temperature when no growth occurred, and both being most effective when slow growth occurred either at room temperature or at 41 C., and highly effective at ordinary incubator temperature. When the cultures were removed from the refrigerator at the end of ninety hours and placed in the incubator, the control multiplied and the drugs already present were still effective. This experiment suggests that growth of the organisms is essential for the action both of neoarsphenamine and of sulfathiazole.

Hours	Temperature, C.	Control	Neoarsphenamine 0.5 mg. per 100 Cc.	Sulfathiazole, 5 mg. per 100 Cc.
0	41	90	90	90
20	41	225,000,000	0	200,000
44	41	..	0	1,500,000
0	37	90	90	90
20	37	450,000,000	7	2,500,000
44	37	..	0	1,250,000
0	20.7-23.1	90	90	90
20	20.7-23.1	8,000	43	57
44	20.7-23.1	850,000	10	37
90	20.7-23.1	320,000,000	0	3
116	20.7-23.1	..	7	3
0	3.3-4.7	90	90	90
20	3.3-4.7	120	128	175
44	3.3-4.7	140	125	120
90	3.3-4.7	80	77	93
116	37	400,000,000	3	1,200,000

salivarius. The two exceptions were identified as *Streptococcus faecalis*, one of which responded only to neoarsphenamine and the other only to sulfathiazole.

#### MECHANISM OF ACTION

One of the many experiments on the effects of temperature on the action of these drugs is summarized in table 6. At refrigerator temperature staphylococci failed to grow, and neoarsphenamine and sulfathiazole were ineffective against the inoculums. When these same cultures were placed in the incubator the bacteria in the control multi-

6. Sears, H. J.; Osgood, E. E., and Joski, J.: The Correlation Between Susceptibility to Neoarsphenamine and Sulfathiazole in Vitro and Certain Other Characteristics of Streptococci from Subacute Bacterial Endocarditis, to be published.

plied and the drugs were effective. At 41 C. the drugs were somewhat more effective than at body temperature, which suggests that a trial of fever therapy in conjunction with the use of neoarsphenamine and sulfathiazole would be worth while. The differences, however, were relatively slight.

Since vitamin C has been reported to reduce the clinical toxicity of neoarsphenamine and the action of neoarsphenamine has been reported to be due to its effect on glutathione, these compounds were tested in marrow cultures. Neither of them led to decreased toxicity of neoarsphenamine for marrow cells or to decreased effectiveness of the drug against the staphylococci. If anything, neoarsphenamine with added glutathione or vitamin C was somewhat more effective than it was in identical cultures without added glutathione or vitamin C. Addition of hydrogen peroxide, an oxidizing agent, or of sodium formaldehyde sulfoxylate, a reducing agent, did not increase the effectiveness of either neoarsphenamine or sulfathiazole, nor were these agents in concentrations which could occur in the body effective by themselves in controlling the infection in marrow cultures. Since other organic arsenicals were not as effective as neoarsphenamine and since an equivalent amount of arsenic in the form of arsenic trioxide was not as effective, it seems possible that the arsenic is not essential and that compounds with sulfur or nitrogen in the position that arsenic occupies in the neoarsphenamine molecule should be investigated. Since definite morphologic changes occurring in the micro-organisms are similar to those which have been observed after therapy with drugs of the sulfanilamide group, it appears that the action is directly on the organism. Added paraaminobenzoic acid does not interfere with the action of neoarsphenamine, as it does with the action of the drugs of the sulfanilamide group.

The action of neoarsphenamine resembles that of a drug of the sulfanilamide group in that a considerable period is required for sterilization, there is an initial lag period and neither agent is effective at refrigerator temperature, when no growth occurs. It is possible that the action of neoarsphenamine and that of the drugs of the sulfanilamide group will prove to be similar, but the exact nature of this action is still undetermined.

#### PRINCIPLES WHICH SHOULD GOVERN THE CLINICAL USE OF NEOARSPHENAMINE

Certain principles which should govern the clinical use of neoarsphenamine are apparent. Neoarsphenamine to be effective against bacterial infections should be administered in such a way as to maintain a blood level which corresponds to arsenic levels of 75 to 200 micrograms per hundred cubic centimeters of blood over the greater part of several days. The dose should be accurate, since half the ideal

concentration is ineffective and twice the ideal concentration is toxic to marrow cells over a period of time. The organisms against which neoarsphenamine is definitely superior to sulfanilamide and its available derivatives are the staphylococci and certain of the alpha streptococci. Its use should be limited, for the present at least, to serious infections, since the effective range is near the toxic range and some clinical toxicity is to be anticipated, particularly because of the known wide variations in idiosyncrasy to this drug. Its use in combination with sulfathiazole therapy is probably better against staphylococci and certain alpha streptococci than is either alone. Fever and excess glutathione in combination with neoarsphenamine therapy may prove to increase its effectiveness. The therapy should be continued for several days or weeks after clinical evidence of infection has disappeared, since small numbers of organisms may exist for a time in cultures containing the drug in adequate concentration.

Since Uhley and Katz<sup>7</sup> have shown that neoarsphenamine penetrates fibrin<sup>3b</sup> better than do drugs of the sulfanilamide group, the former drug appears to offer particular advantages over the latter ones in the therapy of subacute bacterial endocarditis and, perhaps, of gonococcic endocarditis. Since de Kruif and Simpson<sup>8</sup> have shown that fever decreases the toxicity of neoarsphenamine and since it is probable that fever therapy will open up more vascular channels, a trial of associated fever therapy with neoarsphenamine should certainly be made.

#### DOSAGE OF NEOARSPHENAMINE NECESSARY TO MAINTAIN UNIFORM BLOOD LEVELS

Development by Chaney and Magnuson<sup>9</sup> of an accurate method for measuring the arsenic in the blood made possible the determination of blood arsenic levels after administration of various doses of neoarsphenamine. In figure 2 the curve of the blood arsenic levels after a single intravenous injection of neoarsphenamine is given. The curve is of the logarithmic type and forms a straight line on logarithmic paper. The arsenic of neoarsphenamine is distributed evenly throughout the blood a few minutes after administration but rapidly leaves the blood, and by four hours after administration the blood concentration is that which would be expected if the drug was distributed

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7. Uhley, M. H., and Katz, L. N.: An in Vitro Test for Chemotherapeutic Agents Used in Subacute Bacterial Endocarditis, *J. Infect. Dis.* **68**:291-300 (May-June) 1941.

8. de Kruif, P., and Simpson, W. M.: Possible Significance of the Inhibitory Effect of Fever on Anaphylactic Phenomena, *J. Lab. & Clin. Med.* **26**:125-130 (Oct.) 1940.

9. Chaney, A. L., and Magnuson, H. J.: Colorimetric Microdetermination of Arsenic, *J. Indust. & Engin. Chem. (Analyt. Ed.)* **12**:691-693 (Nov.) 1940.



approximately evenly throughout the body volume. After four hours the rate of elimination is much slower but may still be expressed by a logarithmic curve. From these curves the blood arsenic levels may

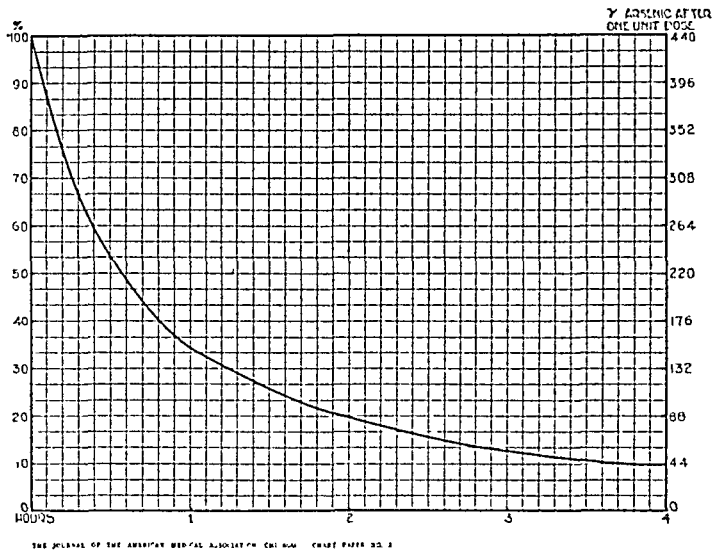


Fig. 2.—The logarithmic curve giving the blood arsenic levels in percentage of the initial concentration and in micrograms per hundred cubic centimeters after injection of a single unit dose of neoarsphenamine during the first four hours. After the first four hours the rate of decrease is even slower but may still be expressed by a logarithmic curve.

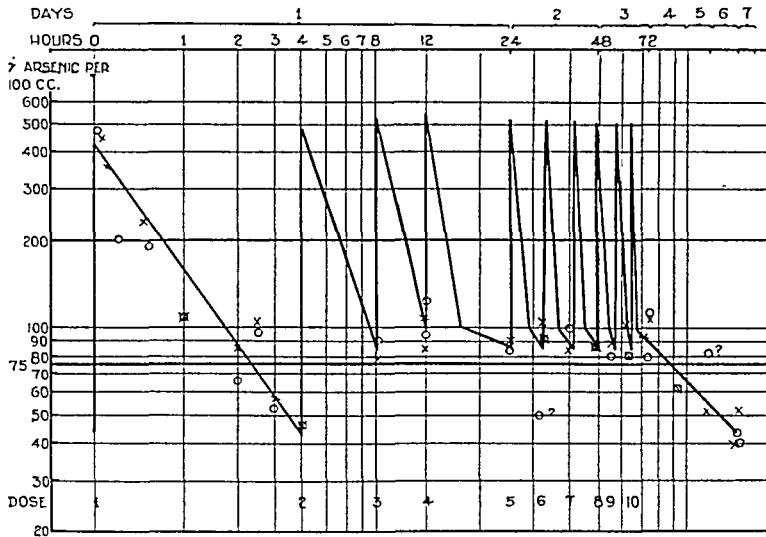


Fig. 3.—Calculated blood arsenic levels plotted on logarithmic paper during a typical three day course, against which are plotted the actual determinations for 2 patients receiving neoarsphenamine according to the schedule in table 7. The blood arsenic levels are the same as those on the second and third day if the course is continued for a longer period. X, blood arsenic determinations for a patient whose weight was 126 pounds (57.2 Kg.); O, blood arsenic determinations for a patient whose weight was 158 pounds (72 Kg.).

be predicted accurately if the weight of the patient, the time and amount of neoarsphenamine given and the time which has elapsed since the neoarsphenamine was given are known. This may not apply to patients with impairment of renal function for whom blood arsenic levels have

TABLE 7.—*Method of Administration of Neoarsphenamine*

The unit dose is 0.8 mg. per pound of body weight; e. g., if the weight of the patient is 150 pounds,  $150 \times 0.8 = 0.12$  Gm. Therefore, each unit dose for this patient is 0.12 Gm. of neoarsphenamine, freshly prepared from a 0.15 Gm. ampule.

Time Schedule for Each Unit Dose										
Course X: First course for acute staphylococcal infections										
Course Y: First course for subacute bacterial endocarditis and chronic staphylococcal infections										
Course Z: Each subsequent course for subacute bacterial endocarditis and chronic staphylococcal infections										
Day of course.....	1	2	3	4	5	6	7	8	9	10
Hour 8 a.m. ....	1	5	8	11	14	17	20	23	26	29
12 a.m. ....	2									
4 p.m. ....	3	6	9	12	15	18	21	24	27	30
8 p.m. ....	4									
12 p.m. ....		7	10	13	16	19	22	25	28	31

TABLE 8.—*Schedule of Courses of Therapy for Subacute Bacterial Endocarditis or Chronic Staphylococcus Infections*

Days	Days of Therapy with Neoarsphenamine	Rest	Neoarsphenamine	
1-6	6	..	Course Y	Table 7
7-9	..	3	None	
10-12	3	..	Course Z	Table 7
13-15	..	3	None	
16-18	3	..	Course Z	Table 7
19-22	..	4	None	
23-25	3	..	Course Z	Table 7
26-30	..	5	None	
31-33	3	..	Course Z	Table 7
34-39	..	6	None	
40-42	3	..	Course Z	Table 7
43-48	..	6	None	
49-51	3	..	Course Z	Table 7
52-57	..	6	None	
58-60	3	..	Course Z	Table 7

not yet been determined. Details of the use of the curves and the equations derived from them will be published elsewhere. From these curves it is calculated that small doses of neoarsphenamine should be given at four hour intervals until the level at four hours after the last dose is within the effective range, and then doses should be given at longer intervals.

From these data a method of administration of neoarsphenamine which maintains uniform blood levels has been developed. The unit dose is 0.8 mg. per pound (0.5 Kg.) of body weight. Details of the administration are given in tables 7 and 8. One unit dose is given every four hours the first day for four doses and then every eight hours for three doses each subsequent day for the duration of the course. In figure 3 the calculated curve of blood arsenic levels during a typical three day course and during the subsequent three day rest period is compared with the actual blood arsenic levels determined for 2 patients of widely different weights being treated for primary syphilis by this method.

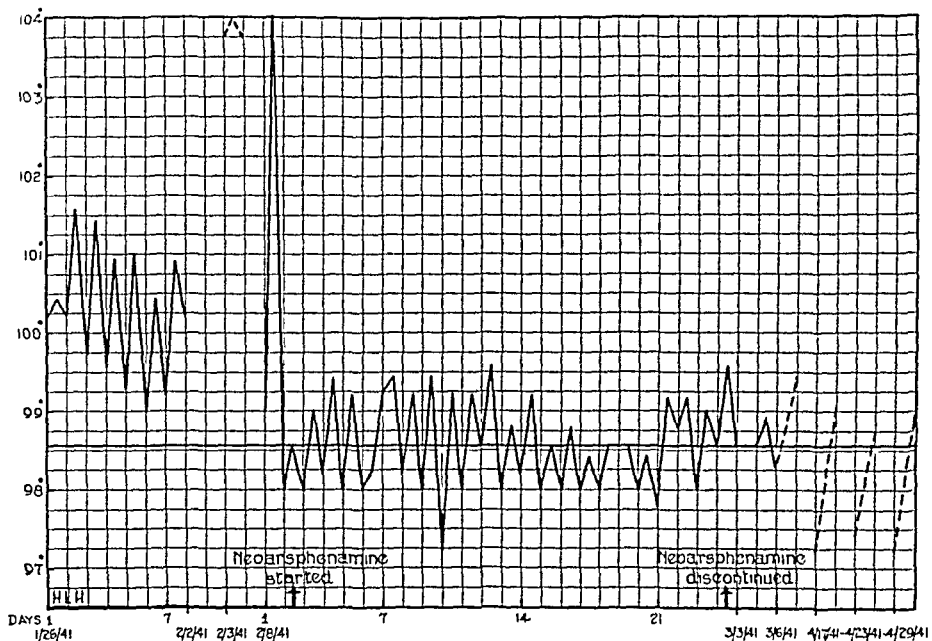


Fig. 4.—A typical temperature curve in a case of subacute bacterial endocarditis caused by an alpha streptococcus belonging to group A and responding to neoarsphenamine. In this case the patient had received sulfathiazole previously, with no effect on the temperature. At the present time the patient is free from symptoms of the disease. When such a temperature response is obtained in the first six days of therapy neoarsphenamine alone is given, even though marrow culture studies are not available to place the organism in the group in which it belongs, since the response can be obtained more quickly than results of marrow culture studies and since bacteriologic methods have not yet been developed that will determine what the response to neoarsphenamine will be.

#### SUGGESTED THERAPY FOR SERIOUS STAPHYLOCOCCIC INFECTIONS, SUB-ACUTE BACTERIAL ENDOCARDITIS AND, POSSIBLY, SYPHILIS

Neoarsphenamine is given as outlined in table 7, course Y. If there is a marked fall in the temperature and the clinical condition is improved

by the end of course Y, the organism belongs to group A or B and neoarsphenamine should be continued as outlined in table 8. If there is no response in the first six days <sup>9a</sup> the organism belongs to group C and neoarsphenamine should be discontinued and sulfathiazole administered at four hour intervals, day and night, in doses sufficient to maintain a blood level of 5 to 8 mg. per hundred cubic centimeters for a period of sixty days or longer. If there is some response by the end of the sixth day (table 7, course Y) the organism belongs to group B and sulfathiazole should be started at once and neoarsphenamine continued as outlined in table 8. The initial six day period of therapy is a test period to determine by the clinical course and temperature response

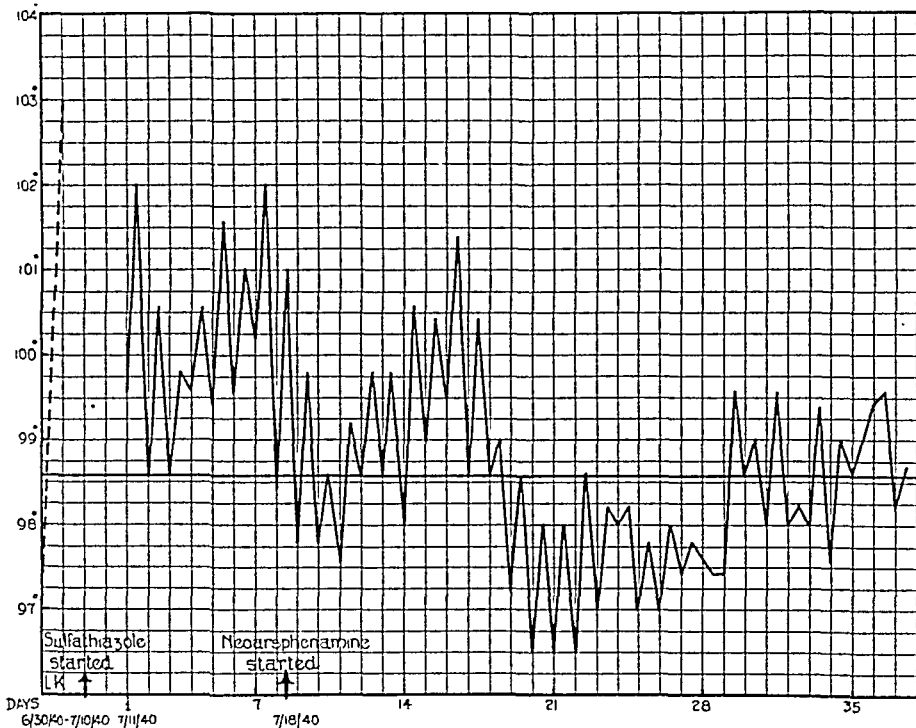


Fig. 5.—A type of temperature curve in a case of subacute bacterial endocarditis suggesting that the causative alpha streptococcus belongs to group B, although this was not determined by marrow culture studies. In this case the patient received both neoarsphenamine and sulfathiazole and was free from symptoms and had blood cultures negative for the causative organism eleven months after therapy was started. Although symptoms of cirrhosis developed within three days after therapy was started they were apparently unrelated to the therapy, and the administration of the drug was continued. The patient died suddenly on June 20, 1941, from an apparently unrelated cause, and permission for autopsy was refused. Dr. A. M. Hoffman, of Los Angeles, permitted me to report this case.

when marrow culture studies are not available (figs. 4 to 6) whether neoarsphenamine therapy should be continued.

<sup>9a</sup>. Now twenty-five days. See the note at the end of the paper.

If tooth extraction is unavoidable for a patient with rheumatic heart disease or congenital heart disease a Z course (table 7) of neoarsphenamine therapy with sulfathiazole administered both orally and locally<sup>10</sup> may be justified for prophylaxis against subacute bacterial endocarditis.

The ideal length of treatment and the ideal length of the rest periods or whether any rest periods should be given is not yet known. It is hoped that other investigators will aid in determining these factors.

#### CLINICAL OBSERVATIONS

It has been shown that neoarsphenamine therapy alone will result in cure in some cases of staphylococcic bacteremia.<sup>11</sup> Whether neo-

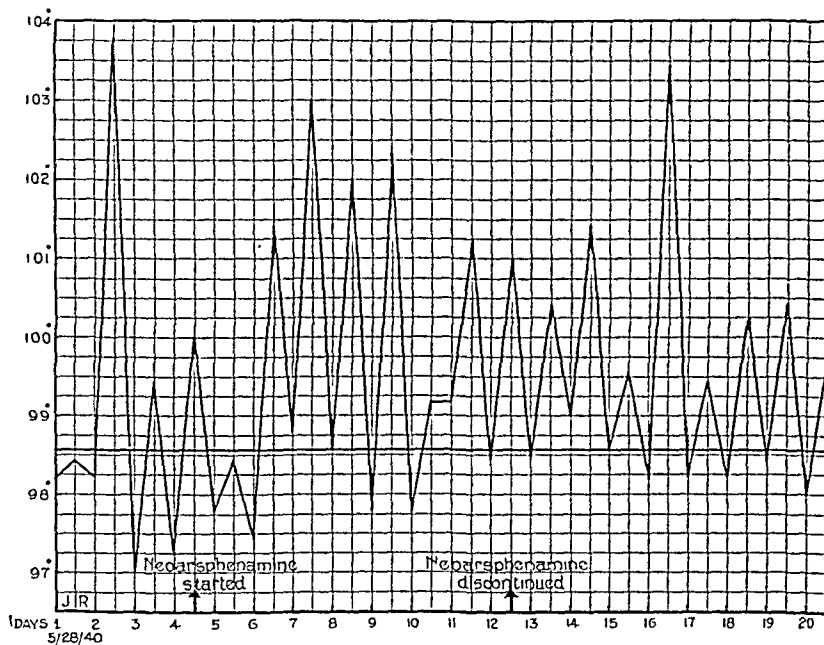


Fig. 6.—A type of temperature curve characteristic of subacute bacterial endocarditis caused by a streptococcus of group C. Note that there is no response whatsoever when neoarsphenamine is given; so this drug should be discontinued after the first six days, and sulfathiazole, sulfadiazine or sulfapyridine should be given. In this patient toxicity to sulfathiazole prevented continuation of treatment. Dr. L. A. Goldsmith, of Portland, Ore., permitted me to report this case.

arsphenamine alone, neoarsphenamine plus sulfathiazole or sulfathiazole alone will ultimately prove the ideal therapeutic agent for staphylococcic infections of a serious nature must still be determined. This will

10. Meacham, P. L., and Osgood, E. E.: The Efficacy of the Local Use of Sulfathiazole Powder in Dentistry and Oral Surgery, *J. Am. Dent. A.* **28**:1640-1644 (Oct.) 1941.

11. LeCocq.<sup>2</sup> Osgood and others.<sup>3</sup>

necessitate study of a large series of cases of staphylococcic bacteremia in which each of the three therapeutic agents is alternated and sulfathiazole is applied locally to any collection of pus, according to the principles previously given.<sup>12</sup> From the experimental data it is probable that neoarsphenamine plus sulfathiazole will prove the best.

Too few cases of subacute bacterial endocarditis have been studied, and for too short a time, to permit any final appraisal, but in 4 cases in which treatment was with neoarsphenamine or neoarsphenamine and sulfathiazole anemia, petechiae and fever completely disappeared, blood

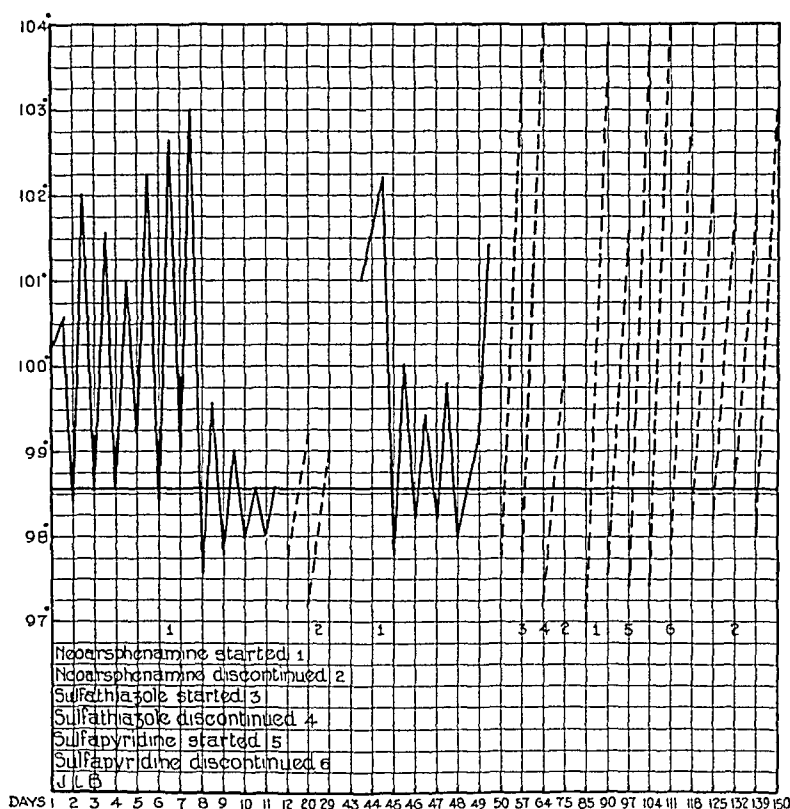


Fig. 7.—The case of subacute bacterial endocarditis represented in this figure demonstrates that the schedule given in table 7 must be followed accurately if adequate concentrations of arsenic are to be maintained in the blood. In this case the patient was first treated before the correct dosage for neoarsphenamine was developed. He had an immediate temperature response to the inadequate dose, but the blood cultures never became negative for the causative organism. After the period of treatment, with sulfathiazole, which produced severe toxicity and little benefit, neoarsphenamine in adequate dosage was given, with no effect. A total of 16.7 Gm. of neoarsphenamine was given with no evidence of toxicity. The organism isolated after the second period of treatment responded poorly to neoarsphenamine in comparison with the initial response, which suggested that it had become arsenic fast. The patient died on Oct. 10, 1940. Dr. B. O. Woods, of Portland, Ore., permitted me to report this case.

12. Osgood, E. E.: Chemotherapy, Arch. Otolaryng. **33**:961-968 (June) 1941. Meacham and Osgood.<sup>10</sup>

cultures became negative and symptoms of the disease were absent for eight to sixteen months. In none of these cases was the patient treated with heparin. These patients have obviously not been studied long enough to justify any claim that subacute bacterial endocarditis can be cured by such therapy, but this observation would seem to justify further trial of the treatment by other investigators. It will certainly not be curative in cases of subacute bacterial endocarditis due to organisms belonging in group C, and to date in those cases in which there was no response to neoarsphenamine so much toxicity from sulfathiazole or sulfapyridine therapy has developed that the drug had to be discontinued. Accord-

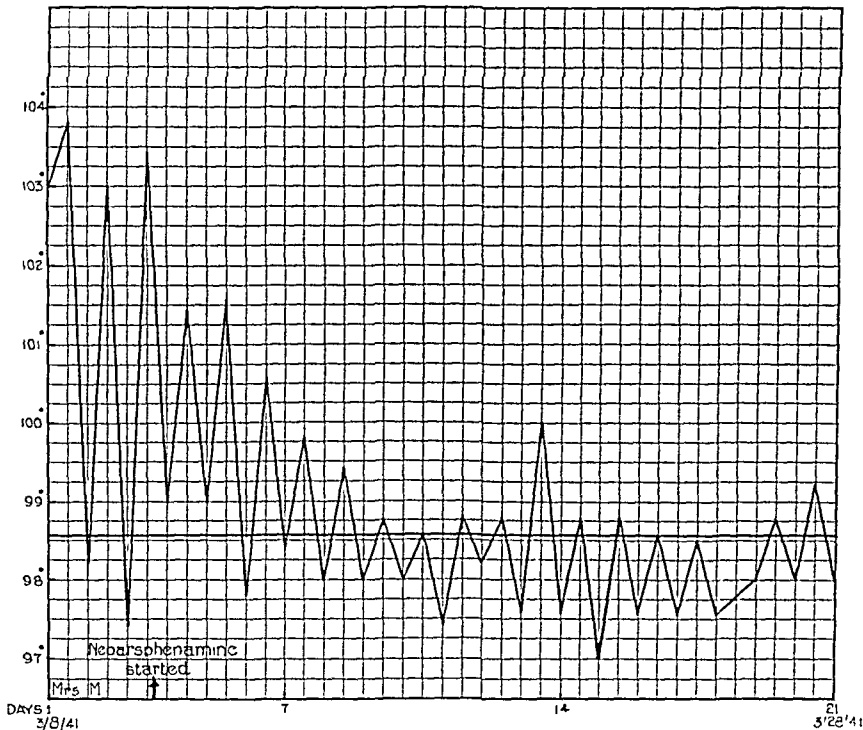


Fig. 8.—The case represented in this figure illustrates the fact that the schedule given in table 7 must be followed accurately if adequate concentrations of arsenic in the blood are to be maintained. This patient had subacute bacterial endocarditis, had had a major cerebral embolus and was almost moribund before therapy was started. Even at such a late stage neoarsphenamine produced striking clinical improvement and improvement in the temperature curve. The patient died suddenly from a ruptured mycotic aneurysm at the site of the cerebral embolus. At necropsy the lesion on the heart valve was healing but was not completely healed. In marrow cultures the organism responded both to neoarsphenamine and to sulfathiazole, and it was therefore classed in group B. Dr. C. D. Platner of Sandy, Ore., permitted me to report this case.

ing to the marrow culture data sulfadiazine should be worth trying in such cases in the future.

Prior to the development of a method of administration of neoarsphenamine which would maintain adequate blood levels, several patients with subacute bacterial endocarditis were treated with inadequate or improperly spaced doses. One of these had complete disappearance of symptoms, including anemia and ten blood cultures negative for the causative streptococcus during a three month period, which was followed by recurrence of symptoms and positive blood cultures. This patient died eighteen months after treatment was started and twenty-one months after the onset of the disease. Neoarsphenamine therapy was not repeated because exfoliative dermatitis developed after the previous procedure, which consisted of one course of six injections of 0.1 Gm. each at two hour intervals and five courses of nine injections of 0.1 Gm. each at two hour intervals, with five days intervening between

TABLE 9.—*Clinical Evidences of Toxicity*

Indications for Discontinuation of Drug	
Neoarsphenamine *	Drugs of the Sulfanilamide Group
Hemorrhagic encephalitis	Agranulocytosis
Exfoliative dermatitis	Hemolytic anemia
Agranulocytosis	Oliguria
Aplastic anemia	Hepatitis
Polyneuritis	Neuritis
Hepatitis	Dermatitis
Indications for Weighing the Risk of the Disease Against the Risk of the Therapy	
Fever	Conjunctivitis
Vomiting	Fever
Nausea	Vomiting
	Nausea

\* Neither vitamin C nor glutathione decreases the toxicity of neoarsphenamine for marrow cells or the effectiveness of neoarsphenamine against staphylococci.

each course. This dosage, it is now known, would produce too high a blood level for too short a time.

The other patient had two unit doses a day, instead of the three now recommended, for three weeks, without rest periods. There was marked clinical improvement, and he was afebrile for a month, but the blood cultures never became negative for the causative organism, and it was subsequently arsenic fast both clinically and in marrow cultures (fig. 7).

One patient died before neoarsphenamine therapy was completed (fig. 8). She had had subacute bacterial endocarditis for one year and a major cerebral embolus shortly before therapy was started. Marked improvement in the temperature and clinical condition occurred. Death was sudden and was shown at necropsy to be due to rupture of a mycotic aneurysm at the site of the cerebral embolus. The valve lesion was healing but not completely healed.



## CLINICAL TOXICITY

The toxic effects of neoarsphenamine and sulfathiazole are well known (table 9). Since the level necessary for effectiveness is near the toxic level, some toxicity is to be anticipated with these therapeutic agents. With the dosage recommended mild degrees of polyneuritis and dermatitis have been observed, and they have necessitated stopping the drug. Because of wide variations in individual idiosyncrasy to the drug, some toxicity from neoarsphenamine therapy with any method of administration ought to be anticipated. The patient should be watched closely for any of the toxic manifestations mentioned in table 9. Toxicity to sulfathiazole has been observed more frequently in patients with subacute bacterial endocarditis than in patients treated for any other disease, which may be a coincidence. It may mean that because of its lesser toxicity sulfadiazine will prove to be the superior drug clinically. Some patients who had toxic reactions to sulfathiazole have been able to take neoarsphenamine without untoward effects.

## SUMMARY

Neoarsphenamine in concentrations which do not kill living human cells is effective against some strains of *Str. viridans*, most staphylococci and some other bacteria.

The effective concentration can be maintained clinically by the method described.

The blood arsenic levels after intravenous administration of neoarsphenamine may be predicted from curves shown in figures 2 and 3.

A few patients with staphylococcic bacteremia so treated have recovered.

A few patients with subacute bacterial endocarditis so treated are free from symptoms of the disease from eight to sixteen months after therapy. More patients must be followed for two years or longer before final appraisal is justified.

The ideal duration of therapy and the length of rest periods are not yet known.

The therapy involves risk of toxicity and should be used only in cases of serious infection or under careful research supervision.

Neoarsphenamine plus sulfathiazole may be more effective against certain bacteria than either alone.

Neoarsphenamine and related compounds deserve further study in the therapy of bacterial infections.

NOTE.—Since this article was submitted for publication, the clinical data on patients with subacute bacterial endocarditis have been analyzed in more detail and brought up to date. Of 34 unselected patients, for

whom detailed protocols are available, 4 remained free of symptoms of the disease and 12 had temporary clinical improvement, with return of the temperature to normal. Only 11 patients received therapy at least approximately, and of these, only 7 received it exactly as directed in tables 7 and 8; the 4 symptom-free patients were among the 11, and 3 of these 4 patients were among the 7. These 3 patients are still completely free of symptoms and are pursuing their usual occupations as a woman physician, a farmer and a high school student, eight, thirteen and seventeen months, respectively, after therapy was started, and the fourth patient is described in figure 5. Not included in this report are 36 patients for whom detailed protocols have not been received, 6 of whom I have been informed have been symptom free for several months.

No patient treated only with drugs of the sulfanilamide group showed more than temporary improvement. It is now recommended that neoarsphenamine therapy, as outlined in table 8, not be discontinued before twenty-five days, even though there is no earlier clinical evidence of benefit. I am also now giving 100 mg. of ascorbic acid and 40 mg. of thiamine hydrochloride daily during neoarsphenamine therapy, with the hope of decreasing toxicity. It is also thought advisable not to discontinue neoarsphenamine for mild polyneuritis or dermatitis.

#### ABSTRACT OF DISCUSSION

DR. LOUIS N. KATZ, Chicago: My remarks will be confined to subacute bacterial endocarditis. While physicians know the causative organism and recognize that the patient will succumb to the disease, so far they can do nothing about it. Any attempt to cure patients with this disease is worth exploring, and for this reason Dr. Osgood's report deserves attention.

My colleagues, Drs. Hamburger, Friedman, Howell and Uhley, and I have been interested in this subject for several years. Fundamentally subacute bacterial endocarditis is due to the organisms located within the vegetations on the valve. The aim, therefore, should be to prevent the deposition of new fibrin on the vegetation and to obtain a sufficient concentration of antiseptic or bacteriostatic drugs in the vegetation, where the organisms reside. My associates and I employed heparin for the first purpose and are still using it occasionally. However, the results are disappointing. As far as we know no cure has resulted; only at autopsy is there the appearance, on occasion, of healing of some of the vegetations.

As far as bactericidal agents are concerned, we have used sulfanilamide and its derivatives in vitro in fibrin cultures of *Str. viridans*, and our results parallel the in vitro results of Dr. Osgood. We have also tested neoarsphenamine in vitro in fibrin cultures and found it to be effective.

In applying these results to subacute bacterial endocarditis in man, it must be remembered that the drug has to be maintained for long periods at a level toxic to the organism in the vegetation without at the same time being deleterious to the patient. I should like to ask Dr. Osgood if that is the reason that he insists on his particular regimen of neoarsphenamine administration.

Sulfanilamide and its derivatives have been used more extensively than have the arsphenamines. It is doubtful whether any cures have resulted from their use.

Recently we used a combination of heparin administered for six weeks, sulfa-pyridine up to toxic doses and mapharsen given in continuous injection until symptoms of hepatic damage appeared. The patient so treated survived therapy for several months but was not cured.

One must be cautious not to build up on the part of physicians and patients expectations as regards cure of this disease which later are dissipated. I should like, therefore, to ask Dr. Osgood whether the experience of others with his method is as good as his own results. Are the results more favorable than the expected remissions which occur in this disease?

Whenever any new method is suggested, it should first be given a trial in the laboratory or test tube, as Dr. Osgood and we have done, before patients are subjected to it. When it is used on a patient, the question of possible ill effects and discomfort must be weighed against the possible benefits. All studies, like those by Dr. Osgood, by us and by others, are in the nature of clinical experimentation, and the final judgment as to which therapeutic agent, if any, will be useful will have to wait the test of time. Frankly, our own clinical experiments have been extremely disappointing, but this does not mean that further trials are not warranted.

DR. C. M. GRUBER, Philadelphia: If there is no further discussion, I should like to ask Dr. Osgood one question: Just how does the neoarsphenamine act, since it apparently does not act through the arsenic? It is thought, for example, the neoarsphenamine is changed to arsenoxide, and the arsenoxide then is the active part. It looks as if this must act as a whole molecule. Will you also answer that, please?

DR. EDWIN E. OSGOOD, Portland, Ore.: Dr. Katz's observation that neoarsphenamine penetrates fibrin better than do drugs of the sulfanilamide group is an important one and may explain the fact that my colleagues and I have had better results with neoarsphenamine than we have with the sulfanilamide drugs.

The 4 patients who have been free of symptoms for eight to sixteen months represent all the patients, with 1 exception, cited in the paper, that have been treated by the method we now recommend who showed a drop in temperature and clinical response within the first six to ten days. During that time about an equal number of patients whose infecting organism was not affected by neoarsphenamine clinically or in marrow cultures were treated with sulfathiazole, and none of these patients has recovered. Prior to July 1, 1940, when the dosage which would maintain adequate blood arsenic levels for an adequate period was determined, several patients who were treated with neoarsphenamine inadequately had marked clinical improvement for one to three months but subsequently relapsed. There is no question but that a long time, at least two years, must elapse before a statement in regard to cure is justifiable.

In regard to toxicity, mild polyneuritis occurred in 1 patient and mild dermatitis in another. Before the correct clinical dosage was determined 1 case of severe exfoliative dermatitis developed. The therapy has not been used with enough patients to permit us to predict the toxicity of the agent accurately. It should be intermediate between that associated with the continuous drip therapy and that associated with the standard treatment for syphilis.

In regard to the question about the way in which we derived this particular dosage, it was based on the fact that neoarsphenamine leaves the blood fairly rapidly during the first four hours after administration; then the rate of elimination is much slower, and the level in the blood is proportional to the blood volume and body weight. So by giving a dose based on body weight every four hours

for the first four doses the level can be built up to within the effective range at the end of four hours, and there is still no time, except for a short period after the first dose, from the moment of giving the first dose when the blood level is not in effective range. While it is true that theoretically continuous drip therapy would give a more uniform level if it were continued twenty-four hours a day, the method of administration I have recommended is simpler and maintains a level within the effective range continuously. The levels and the curves were based on over 100 determinations of blood arsenic for patients of widely different weights, and we find good agreement between this theoretic curve and the actual blood arsenic levels. I do not have time to present them here, but we have equations from which we can predict, within about  $\pm 20$  per cent, the blood arsenic level for any patient so far studied if the body weight, the time of administration of the last dose of neoarsphenamine, the amount of neoarsphenamine in each dose and the intervals between doses previously given are shown.

In regard to the question about the mechanism of action, from a great deal of work already done we feel that the action is directly on the organism, that it may well not be due to the arsenical part of the radical because none of the other arsenicals tested has been as effective and that it apparently is not due to the sulfoxalate group because sodium formaldehyde sulfoxalate was not effective. I plan to investigate the effectiveness of compounds similar to neoarsphenamine but with sulfur or nitrogen substituted for the arsenic and drugs of the sulfanilamide group with arsenic substituted for sulfur.

The effect of temperature has been given in the paper. Growth of the organisms is essential for the action. Fever with neoarsphenamine may be somewhat more effective than is neoarsphenamine alone. The action is not due to phagocytosis; there are morphologic changes in the organisms; the action does take time, and the concentration has to be extremely accurate. Half as much is not effective; twice as much is toxic. We know that paraaminobenzoic acid does not interfere with the action of neoarsphenamine as it does with the action of drugs of the sulfanilamide group. Administration of oxidizing or reducing agents with neoarsphenamine does not greatly affect the activity in concentrations that would be possible to obtain in the human body. Vitamin C added with the neoarsphenamine to marrow cultures does not decrease the activity or the toxicity, which, of course, does not prove that it would not decrease toxicity in the human body. Glutathione plus neoarsphenamine in our cultures is more effective than is neoarsphenamine alone. We have not used it in combination with neoarsphenamine in the clinic.

# CLINICAL STUDIES OF DRUG ADDICTION

## PHYSICAL DEPENDENCE, WITHDRAWAL AND RECOVERY

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The mechanisms of tolerance to and dependence on narcotic drugs are not known, but the studies of Light and Torrance<sup>1</sup> furnished ample proof that the addict can withstand tremendous amounts of morphine and that while receiving morphine in amounts adequate to his addiction needs, the addict is practically normal from a physiologic point of view.<sup>2</sup> Withdrawal of morphine, however, precipitates a characteristic syndrome of signs and symptoms indicating significant disturbance of many body functions.<sup>3</sup> After a few stormy days the recovery process becomes evident, and after several weeks patients appear to have recovered physically. However, the clinical impression at this hospital has been that six to nine months of total abstinence is requisite to adequate recovery. Since objective data on the recovery process were needed to establish this, a longitudinal study was undertaken in which a number of observations were made on a group of patients during the last week of addiction, the first fifteen consecutive days following withdrawal and at thirty day intervals to the ninth month of abstinence. It was thought that such a study would give information not only on the rate of recovery but on the completeness of adjustment of various functions to narcotic

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From the United States Public Health Service Hospital.

1. Light, A. B., and Torrance, E. G.: Opium Addiction: Effects of Intramuscular and Intravenous Administration of Large Doses of Morphine to Human Addicts, *Arch. Int. Med.* **44**:376 (Sept.) 1929.

2. (a) Light, A. B., and Torrance, E. G.: Opium Addiction: Physical Characteristics and Physical Fitness of Addicts During Administration of Morphine, *Arch. Int. Med.* **43**:326 (March) 1929; (b) Opium Addiction: Circulation and Respiration of Human Addicts During Administration of Morphine, *ibid.* **43**:556 (April) 1929. (c) Karr, W. G.; Light, A. B., and Torrance, E. G.: Opium Addiction: Blood of Human Addict During Administration of Morphine, *ibid.* **43**:684 (May) 1929. (d) Light, A. B., and Torrance, E. G.: Opium Addiction: Miscellaneous Observations on Human Addicts During Administration of Morphine, *ibid.* **43**:878 (June) 1929.

3. Light, A. B., and Torrance, E. G.: Opium Addiction: Effects of Abrupt Withdrawal Followed by Readministration of Morphine in Human Addicts, with Special Reference to Composition of Blood, Circulation, and Metabolism, *Arch. Int. Med.* **44**:1 (July) 1929. Kolb, L., and Himmelsbach, C. K.: Clinical Studies of Drug Addiction: Critical Review of Withdrawal Treatments with Method of Evaluating Abstinence Syndromes, *Am. J. Psychiat.* **94**:759 (Jan.) 1938.

drugs. The latter information might be helpful in understanding tolerance and physical dependence.

#### MATERIAL AND METHOD

The subjects selected for this study were cooperative white adult male prisoner or probationer patients, who were physically normal except for valid physical dependence on an opiate at the time of admission. Studies were started on 27 and completed on 21 such patients from Nov. 24, 1936 to Feb. 21, 1941. Eleven of the 21 patients received only morphine; for the remaining 10 certain derivatives<sup>4</sup> were substituted for morphine. Physiologic stability was maintained by the administration of one of these narcotics for at least a week prior to abrupt withdrawal. The following factors were measured during the sequential periods of observation:

*Weight.*—The patient was weighed stripped at 6 a. m., and the weight was recorded in kilograms.

*Caloric Intake.*—The total number of calories ingested daily was estimated from tables of caloric values for foodstuffs. The patients were served weighed amounts of food, and the uneaten portions were weighed prior to disposal. No food was available between meals.

*Sleep.*—Observations were made every half hour, and the total amount of sleep was recorded in hours per day.

*Basal Metabolic Rate.*—This was measured under standard conditions.

*Temperature.*—The rectal temperature (C.) was taken at 6 a. m. and 2 and 7 p. m., and the average of the three determinations was recorded.

*Respiration.*—The rate per minute was noted at 6 a. m. and 2 and 7 p. m., and the average of the three determinations was recorded.

*Blood Pressure.*—The systolic and the diastolic pressure, in millimeters of mercury, was determined at 6 a. m. with the patient recumbent.

*Venous Blood.*—A sample of venous blood was drawn with minimum stasis with the patient in the postabsorptive state, and the levels of dextrose, inorganic phosphorus and lactic acid; the sedimentation rate; the hematocrit reading and the specific gravity were determined. One cubic centimeter of blood was treated with heparin for determining the specific gravity by the method of Barbour and Hamilton,<sup>5</sup> and the remainder of the sample was oxalated by the method of Wintrobe, Shumacker and Schmidt.<sup>6</sup> Blood used for the measurement of inorganic phosphorus was precipitated in trichloroacetic acid within one minute after venipuncture. The values reported for the sedimentation rate are readings made in Wintrobe tubes at one hour; hematocrit readings were made after the tubes were centrifuged at 2,000 revolutions per minute for fifteen minutes.

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4. Dihydrocodeinone enol acetate (acedicon) was substituted for morphine in 2 patients, dihydrocodeine methyl ether (tetrahydrothebaine) for 2, dihydroalpha-isomorphine for 1, alphaisomorphine for 2, dihydroisocodeine for 1 and isocodeine for 2.

5. Barbour, H. G., and Hamilton, W. F.: The Falling Drop Method for Determining Specific Gravity, *J. Biol. Chem.* **69**:625 (Aug.) 1926.

6. Wintrobe, M. M.; Shumacker, H. B., Jr., and Schmidt, W. J.: Values for Number, Size and Hemoglobin Content of Erythrocytes in Normal Dogs, Rabbits and Cats, *Am. J. Physiol.* **114**:502 (Jan.) 1936.

## RESULTS

The results are presented as group means for each factor, measured daily during the last seven days of addiction and the first fifteen days of abstinence and once during each thirty day interval from the thirtieth through the two hundred and seventieth day of abstinence. Curves have been drawn to illustrate the sequential changes in each factor in a longitudinal fashion (figure).

*Weight.*—These data are presented as deviations in kilograms from the weight on the last day of addiction. A steady but small increase in weight occurred during addiction, followed by a 3 Kg. loss shortly after withdrawal. Most of this loss was regained by the fifteenth day of abstinence. The patients continued to gain, and finally the weight reached a plateau 6 Kg. above the addiction level four months after withdrawal. This phenomenon has been reported by Brown.<sup>7</sup>

*Caloric Intake.*—A steady but small increase in appetite occurred during addiction. The anorexia of withdrawal was characteristic. Recovery of appetite was complete within one week; then until the second month of abstinence the caloric intake was greater than during addiction. It then fell to and slightly below the addiction level and remained there.

*Sleep.*—Sleep was somewhat irregular during addiction, the patients averaging about seven hours' sleep out of twenty-four. The sleep "yen" described by Light and Torrance<sup>8</sup> was definite on the first day after withdrawal; the patients thereafter showed the insomnia characteristic of early abstinence. Recovery in sleep was nearly complete by the fifteenth day, but improvement continued until the second month of abstinence; thereafter the patients slept slightly but consistently more than during addiction.

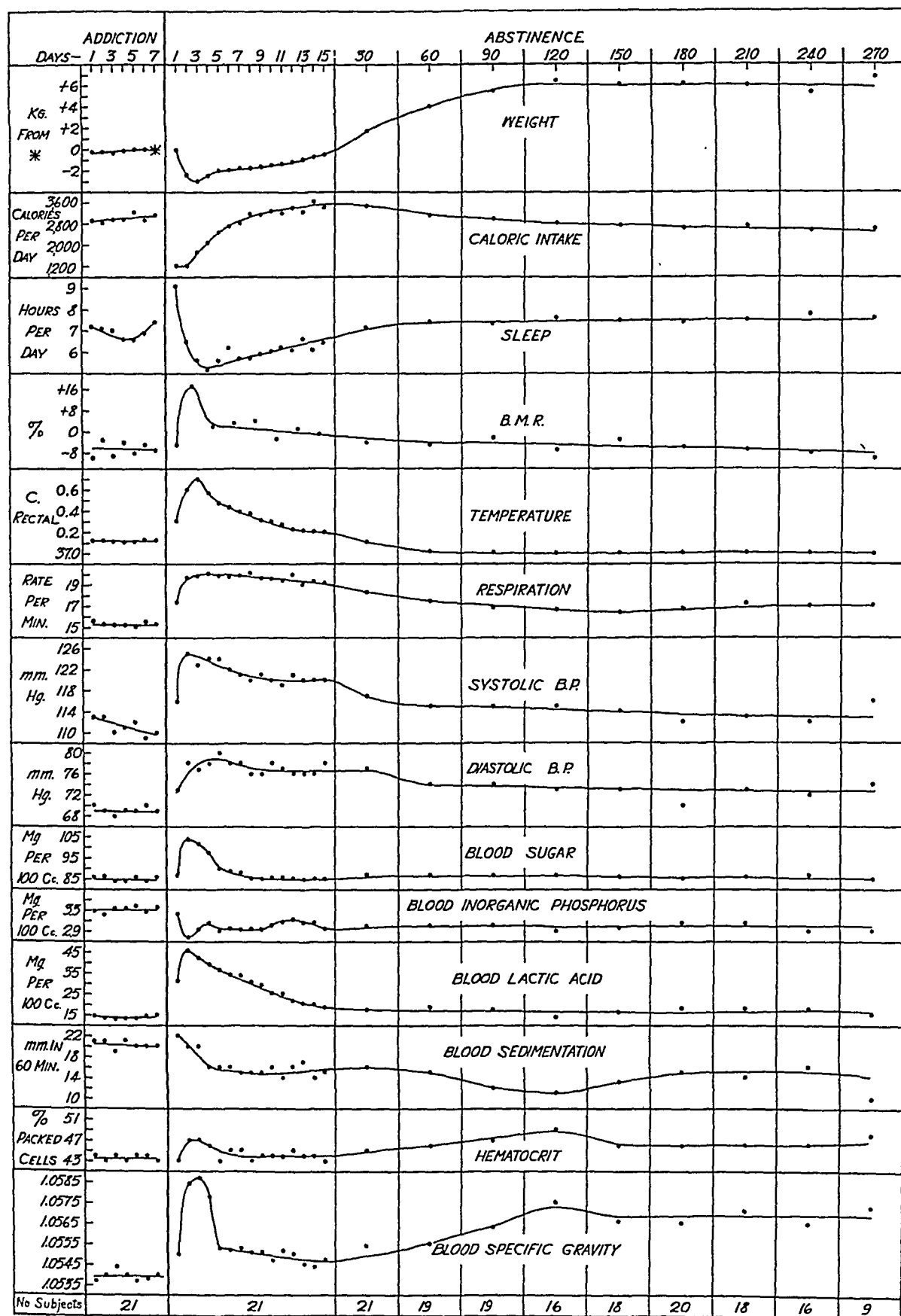
*Basal Metabolic Rate.*—The average basal metabolic rate of this group was about —7 per cent during addiction. A typical rise occurred after withdrawal, and then the basal metabolic rate declined steadily until the addiction mean was regained, by the fourth to the sixth month of abstinence.

*Temperature.*—The average daily temperature of these patients during addiction was 37.1 C. After withdrawal they showed the fever typical of early abstinence. Recovery was complete by the thirtieth day of abstinence, but the temperature fell to 37.0 C. on the sixtieth day and remained there.

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7. Brown, R. R.: Relation of Body Build to Drug Addiction, Pub. Health Rep. 55:1954 (Oct. 25) 1940.

8. Light, A. B., and Torrance, E. G.: Opium Addiction: Conduct of Addict in Relation to Investigative Study, Arch. Int. Med. 43:206 (Feb.) 1929.



Daily group means of measurements made during clinical studies of drug addiction, including physical dependence, withdrawal and recovery.



*Respiration.*—The average respiratory rate of these patients was about 15.3 per minute during addiction. The hyperpnea of withdrawal was characteristic. The addiction level was not regained during the period of study, but the respiration rate leveled off (16 to 17 per minute) by the third month of abstinence.

*Blood Pressure.*—During addiction the mean systolic values ranged from 109 to 113 mm. of mercury, and the diastolic values, from 68 to 70 mm. The pressor effect of withdrawal was typical in both measures. The upper range of the systolic pressure during addiction was regained by the sixth month of abstinence, but the diastolic values tended to level off about 4 mm. above the addiction mean after the fourth month of abstinence.

*Venous Blood Studies.*—Sugar: The range of blood sugar during addiction was 84 to 86 mg. per hundred cubic centimeters. After withdrawal there was a brief period of hyperglycemia. Recovery was complete in eight days, and no further change occurred thereafter.

Inorganic Phosphorus: The addiction level was about 3.3 mg. per hundred cubic centimeters. After withdrawal the level fell to 2.8 mg. per hundred cubic centimeters, then rose to within the range, 2.9 to 3.0 mg., on the third day and remained there.

Lactic Acid: The addiction level of about 15 mg. per hundred cubic centimeters was lower than that found by Karr, Light and Torrance.<sup>2c</sup> A peak of 45 mg. per hundred cubic centimeters was reached on the second day after withdrawal; then the amount of lactic acid in the blood declined steadily and leveled off at about 17 mg. per hundred cubic centimeters after the fifteenth day of abstinence.

Sedimentation Rate: The rate of sedimentation was faster than normal during addiction and was further increased on the first day after withdrawal. This increase was followed by a prompt fall to within the range 14 to 16 mm. per hour, which was maintained until the sixtieth day of abstinence. Then, after a decrease to 11 mm. per hour, the aforementioned range was regained by the sixth month.

Hematocrit Reading: The addiction level, 43 to 44 per cent, and the concentration of the first few days after withdrawal, followed by a return toward the addiction level, and then a rise to a higher range, 46 to 49 per cent, correspond with the results reported by Williams.<sup>9</sup> No further change occurred after the fifth month.

Specific Gravity: The changes in the specific gravity of the blood nearly parallel those described in the paragraph on the hematocrit reading and show hydration during addiction; concentration on the second, third

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9. Williams, E. G.: Blood Concentrations in Morphine Addicts, *J. Pharmacol. & Exper. Therap.* **67**:290 (Nov.) 1939.

and fourth days of abstinence; rehydration, and then recovery by the fourth or the fifth month. The trend of the changes in the specific gravity is similar to that described by Williams.<sup>9</sup>

#### COMMENT

If recovery from physical dependence on narcotics can be assumed to have taken place when equilibrium is regained, these results indicate that physical recovery requires not less than six months of total abstinence. As far as the particular factors studied are concerned, the period of recovery (as represented by the attainment of constant levels in the figure) was not uniform but varied from about one week to about six months. Those factors showing recovery in one month or less were the levels of sugar, inorganic phosphorus and lactic acid in the blood; those taking two or three months were temperature, caloric intake, sleep and respiration, while those requiring four to six months were weight, basal metabolic rate, blood pressure, the hematocrit reading, the sedimentation rate and the specific gravity of the blood. The simplest single index of physical recovery from addiction would seem to be three consecutive monthly measurements of body weight which do not show any upward trend, for the data indicate that after the third month of the weight plateau, no further recovery occurred in any of the factors studied.

Comparison of the data on these patients during addiction with those obtained after recovery indicates that adjustment to morphine is not complete during addiction. Of the fourteen factors studied, only the basal metabolic rate and the level of blood sugar were the same during addiction and after recovery. The tendency of weight to increase during stabilization and the augmented appetite suggest that these patients may not have been receiving an adequate diet prior to admission. Sleep, likewise, may have been disturbed by the process of adjustment to a different environment.

Certain of the deviations of addiction, such as decreased body weight, slightly increased appetite, diminished sleep, elevated body temperature and increased sedimentation rate, would be consistent with augmented metabolism. However, the slowed respiration, the lowered blood pressure and level of lactic acid and the unchanged basal metabolic rate and level of blood sugar do not conform with this. Tatum, Seevers and Collins<sup>10</sup> have advanced the view that morphine simultaneously stimulates certain portions of the nervous system and depresses others. Since the stimulant action outlasts the depressant effect, the former tends to be cumulative with repetitive doses, eventually resulting in a characteristic

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10. Tatum, A. L.; Seevers, M. H., and Collins, K. H.: *Morphine Addiction and Its Physiological Interpretation Based on Experimental Evidences*, J. Pharmacol. & Exper. Therap. **36**:447 (July) 1929.

type of alteration called addiction. This theory, which explains addiction as a strange mixture of stimulation and depression, offers a possible explanation of these results.

The recovery values for the basal metabolic rate and the level of inorganic phosphorus in the blood appear to be subnormal. The average basal metabolic rate in 82 patients (former addicts without hyperthyroidism) in whom this factor was measured for clinical purposes was — 5 per cent. This value is in sufficiently close agreement with the recovery data to suggest that the basal metabolic rate of addicts after recovery is subnormal. Whether this is an irreversible effect of addiction or a characteristic of persons who become addicts cannot be determined from these data.

The inorganic phosphorus in the blood was determined by the method of Youngburg and Youngburg<sup>11</sup> but on whole blood instead of serum. The normal range by this method at this hospital is 2.25 to 3.25 mg. per hundred cubic centimeters. This would indicate that the level of inorganic phosphorus in the blood of addicts during addiction is higher than normal. Karr, Light and Torrance<sup>2c</sup> found the level of inorganic phosphorus in the serum to be subnormal during addiction. Unpublished data on 37 other patients obtained during addiction and the first ten days after withdrawal are in close agreement with the results obtained in this group.

#### CONCLUSIONS

The results of a longitudinal study of 21 persons addicted to morphine or one of its derivatives from the addicted state through withdrawal to the ninth month of total abstinence indicate:

1. The adjustment of physical functions to morphine addiction, while biologically adequate, is incomplete.
2. Physical recovery from addiction is an irregular process requiring approximately six months.
3. A simple measure for the estimation of physical recovery from addiction is weighing the patient at monthly intervals following withdrawal. When no significant increase in weight occurs for three successive months, it appears safe to assume that maximum physical recovery has been reached.
4. The basal metabolic rate of the recovered addict is subnormal.

The following personnel gave technical assistance: Miss Othilia Mertes and Messrs. Ward Workman, Henry Elam, Charles Keebaugh, Robert Blake, Vincent McFadden, Clinton Gray, Charles Allday, Howard Moninger, John Buchanan and Harold Bowhay. The determinations of lactic acid in the blood were made by Mr. Eugene Douglass.

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11. Youngburg, G. E., and Youngburg, M. J.: Phosphorus Metabolism: System of Blood Phosphorus Analysis, *J. Lab. & Clin. Med.* **16**:158 (Nov.) 1930.

# CONCENTRATION OF CARBON DIOXIDE IN EXPIRED AIR

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The concentration of carbon dioxide in the expired air is determined routinely during the estimation of basal metabolism by the open circuit method. This concentration is dependent on the relation of the volume of respired air to the rate of production or elimination of carbon dioxide. The physiologic relation between respiration and the production of carbon dioxide has been summarized by Henderson<sup>1</sup>:

The control of breathing . . . involves many factors: oxygen, carbon dioxide, blood alkali and H ions, and particularly the sensitivity of the respiratory center under a wide range of conditions and influences. For conditions of health the accepted teaching is that of Haldane and his collaborators. It can be summarized in the statement that a normal man . . . breathes . . . *volumes of air that are closely proportional to the amounts of carbon dioxide that are produced in his tissues.* When he sits still, the amount of energy liberated in his body and the amount of carbon dioxide produced are relatively small; and he breathes a correspondingly small volume of air. When he walks about and produces more carbon dioxide, he breathes more air (still) in proportion to the carbon dioxide. In other words, *he ventilates his lungs in close proportion to the energy expended and the oxygen needed but the agent through which the adjustment is made is carbon dioxide.* [The italics are ours.]

Although in clinical medicine the measurement of respiration is of great importance, the methods usually employed are inadequate. The respiratory rate alone is not indicative of the volume of respiration. The minute volume of air breathed takes no account of the size or metabolic activity of the subject. The minute volume per spare meter of surface area offers a correction for size only but not for variation in the metabolic rate. The concentration of carbon dioxide in the alveoli of the lungs measures the relation of alveolar ventilation to carbon dioxide output. However, it is difficult to apply this measurement in clinical medicine.

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1. Henderson, Y.: *Adventures in Respiration*, Baltimore, Williams & Wilkins Company, 1938, p. 49.

## VENTILATION EQUIVALENTS

Within recent years several ventilation equivalents have been proposed for measuring the volume of respiration in relation to the metabolic demand. In 1926, Simonson<sup>2</sup> chose to express the minute volume of respired air per calory of heat produced as the "caloric ventilation equivalent." In 1928, Herbst<sup>3</sup> called the amount of oxygen retained by the body out of 1 liter of inspired air the "utilization coefficient." In 1930, Anthony,<sup>4</sup> also relating pulmonary ventilation to oxygen consumption, described the "ventilation equivalent for oxygen." Marias and McMichael,<sup>5</sup> in 1937, proposed correcting pulmonary ventilation for carbon dioxide production by using the "ventilation equivalent for carbon dioxide." The ventilation equivalents have been called "dilution ratios" by Henderson.<sup>6</sup>

In spite of their sound theoretic bases and the obvious necessity for making such a correction in ventilation measurements, none of these indexes has been widely used. Knipping and Moncrieff<sup>7</sup> have reported studies on the ventilation equivalent for oxygen, using Anthony's formula  $\frac{\text{minute volume in liters} \times 100}{\text{oxygen consumption in cubic centimeters per minute}}$ . In 54 normal subjects they found an average ventilation equivalent of about 2.50, with limits of 1.68 and 2.89, with no apparent difference for sex or age. They concluded that in persons with disease of the circulatory or respiratory system the equivalent is raised roughly in proportion to the degree of failure of function; in patients in a diabetic coma it serves as a delicate indication of the degree of ketosis. Hurtado and Boller<sup>8</sup> found from 15 observations an average ventilation equivalent

2. Simonson, E.: *Zur Physiologie des Energieumsatzes beim Menschen*, Arch. f. d. ges. Physiol. **114**:380, 1926.

3. Herbst, R.: *Der Gasstoffwechsel als Mass der körperlichen Leistungsfähigkeit; die Bestimmung der Sauerstoffaufnahmevermögens beim Gesunden*, Deutsches Arch. f. klin. Med. **162**:33, 1928.

4. Anthony, A. J.: *Untersuchungen über Lungenvolumina und Lungenventilation*, Deutsches Arch. f. klin. Med. **167**:129, 1930.

5. Marias, O. A. S., and McMichael, J.: *Theophylline—Ethylene Diamine in Cheyne-Stokes Respiration*, Lancet **2**:437, 1937.

6. Henderson, Y.: *The Principles Controlling Respiration in Health and Disease*, in Blumer, G.: *The Practitioners Library of Medicine and Surgery*, New York, D. Appleton-Century Company, Inc., 1938, vol. 1, chap. 11.

7. Knipping, H. W., and Moncrieff, A.: *The Ventilation Equivalent for Oxygen*, Quart. J. Med. **1**:17, 1932. Moncrieff, A.: *Tests for Respiratory Efficiency*, Medical Research Council, Special Report Series, no. 198, London, His Majesty's Stationery Office, 1934, pp. 194-205.

8. Hurtado, A., and Boller, C.: *Studies of Total Pulmonary Capacity and Its Subdivisions: I. Normal, Absolute, and Relative Values*, J. Clin. Investigation **12**:793, 1933.

of 2.6, with variations between 1.47 and 4.04 and with a standard deviation of 0.73 (coefficient of variation 28 per cent), and concluded that the variability was too great for clinical value. McMichael<sup>9</sup> in a group of 76 normal subjects found a coefficient of variation of 16 per cent for the oxygen equivalent and 14 per cent for the carbon dioxide equivalent. McMichael also found the ventilation equivalent for oxygen to vary widely with changes in the respiratory quotient while the ventilation equivalent for carbon dioxide remained more constant and

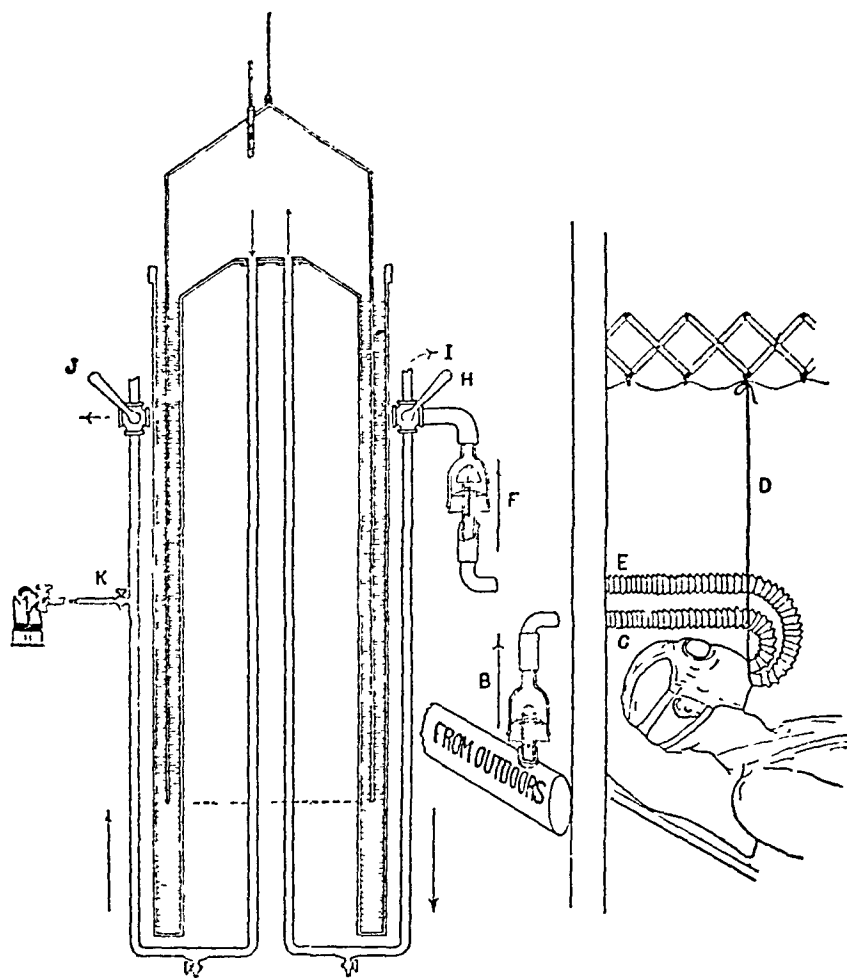


Fig. 1.—Apparatus used in the estimation of basal metabolism (from Bailey<sup>10</sup>).

concluded that the latter was more reliable. It is therefore desirable to submit the principle of ventilation equivalents to a critical examination in large numbers of subjects to determine its reliability and possible clinical significance.

#### METHOD AND MATERIAL

The results presented in this paper have been obtained from basal metabolism determinations made with the Tissot, or open circuit, type of apparatus, in which the subject breathes atmospheric air. The expired air is collected and measured

9. McMichael, J.: Hyperpnea in Heart Failure. *Clin. Sc.* 4:19, 1939.

in a 100 liter gasometer, from which duplicate samples are removed and analyzed with the Haldane-Henderson apparatus. The method as applied in the respiration laboratory of the New York Post-Graduate Medical School and Hospital<sup>10</sup> is illustrated in figure 1. The subject, in a semireclining position, wears a rubber mask<sup>11</sup> which covers the whole face and presents broad surfaces which closely engage the forehead, the sides of the face and the lower jaw. In this mask, the incoming air is directed upward toward the windows and the opening of the expiratory pipe is opposite the mouth and nose. Two foot (61 cm.) lengths of 24 mm. corrugated tubing connect the mask with low resistance air valves.<sup>12</sup> As the subject breathes, the air is drawn from outdoors and passed into the gasometer without conscious effort. The duration of the test is five to twenty-five minutes, depending on the rate of ventilation. Records of over 35,000 basal metabolism examinations personally conducted by one of us (C. V. B.) have been available for this study.<sup>13</sup> Most of the results presented are based on examinations made during the past two years. Additional data have been obtained at times by the use of a portable open circuit type of apparatus and an aliquoting device for sampling the expired air. With this apparatus tests can be continued for a half hour or longer. All subjects have been examined in the basal state, with careful adherence to all conditions found by experience to be necessary for accurate determination of the basal metabolic rate. All respiration studies have been personally conducted by one of us (C. V. B.).

#### CORRELATION OF RESPIRATION WITH METABOLISM

Both oxygen demand and carbon dioxide production can stimulate respiration.<sup>14</sup> Of the two, the production of carbon dioxide is recognized as the more urgent and effective stimulus.<sup>15</sup> On theoretic grounds the volume of respiration should most closely parallel carbon dioxide production. However, other authors have proposed to relate ventilation to heat production and oxygen consumption, as well as to carbon dioxide production. A study has been made of each of these factors in a series of 500 consecutive basal metabolism examinations, excluding as subjects any person having a known cause of respiratory abnormality. The subjects were not restricted as to age, sex or level of basal metabolism. The minute volume of respiration was plotted against surface area, as well as against heat production, oxygen consumption and

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10. Bailey, C. V.: Apparatus Used in the Estimation of Basal Metabolism, *J. Lab. & Clin. Med.* **6**:657, 1921.

11. Bailey, C. V.: Notes on Apparatus Used in Determining the Respiratory Exchange in Man: I. An Adaption of the French Gas Mask for Use in Respiratory Work, *J. Biol. Chem.* **47**:277, 1921.

12. Bailey, C. V.: A Low Resistance Air Valve, *Proc. Soc. Exper. Biol. & Med.* **24**:184, 1926.

13. Dr. Harry Wieder, Mr. Irving Wieder and Mrs. Lee Wieder, members of the staff of the respiration laboratory, gave technical assistance.

14. Haldane, J. S., and Priestley, J. G.: *Respiration*, New Haven, Conn., Yale University Press, 1935.

15. Henderson.<sup>6</sup> Haldane and Priestley.<sup>14</sup>

carbon dioxide production, to determine with which of these factors the volume of respiration is actually most closely correlated. From an inspection of the scatter diagrams (figs. 2, 3 and 4) it may be seen that the minute volume in liters per minute is widely variable. In general, ventilation tends to vary directly with the size of the subject, but the accuracy of ventilation measurements cannot be greatly improved merely by correcting for the surface area. On the other hand, the volume of respiration closely parallels both oxygen consumption and carbon dioxide production.

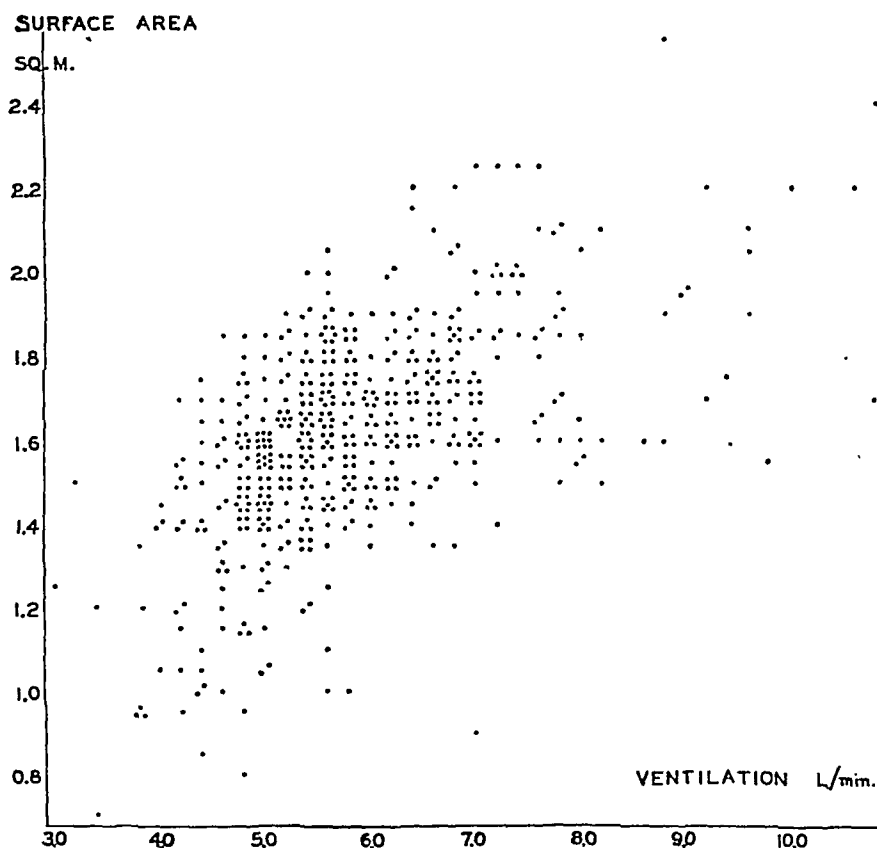


Fig. 2.—The relation of ventilation and surface area in 500 consecutive subjects with known abnormality excluded.

TABLE 1.—*Correlation of Ventilation and Various Factors in Five Hundred Subjects*

	Correlation Coefficient	P.E. <sub>r</sub>
Ventilation and surface area.....	+0.579	±0.0200
Ventilation and oxygen consumption.....	+0.890	±0.0062
Ventilation and heat production.....	+0.903	±0.0059
Ventilation and carbon dioxide production.....	+0.917	±0.0048

Correlation may be demonstrated more precisely by statistical methods than by visual impressions. The correlation coefficient is the



accepted measure for this purpose. As this coefficient approaches unity, the theoretic perfect correlation is present. From an examination of the correlation coefficients calculated from the data on these 500 sub-

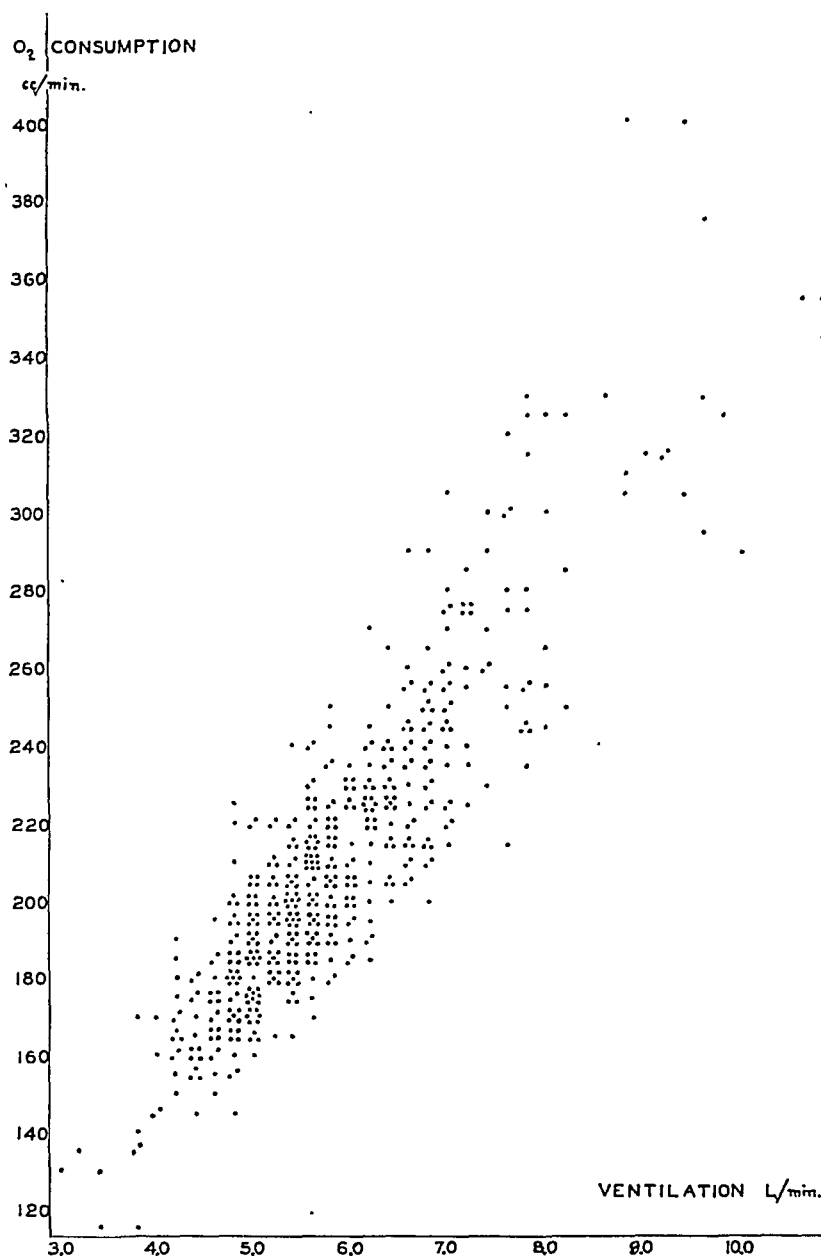


Fig. 3.—The relation of ventilation and oxygen consumption in 500 consecutive subjects with known abnormality excluded.

jects, the association of respiration with surface area is interpreted as being fairly good. The correlations between ventilation and heat production, oxygen consumption and carbon dioxide production are excel-

lent, and of these the correlation with carbon dioxide production is the best.

Although the actual difference between any of the ventilation equivalents is rather small, the ventilation equivalent for carbon dioxide proposed by Marias and McMichael<sup>5</sup> is the most reliable. From an inspection of the usual formulas used in respiration studies, the ventilation equivalent for carbon dioxide is found to be the reciprocal of the concentration of carbon dioxide in the expired air.

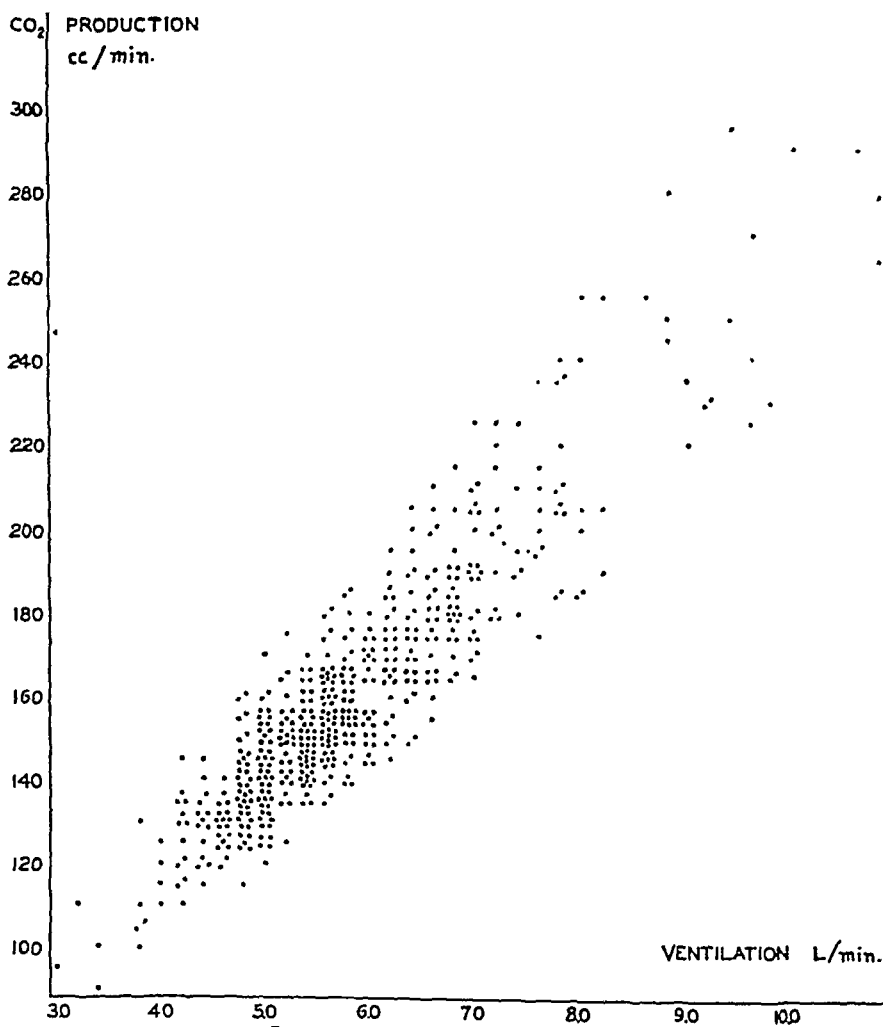


Fig. 4.—The relation of ventilation and carbon dioxide production in 500 consecutive subjects with known abnormality excluded.

Since ventilation ( $V$ )  $\times$   $\text{CO}_2\%$  =  $\text{CO}_2$  production, then  $\frac{1}{\text{CO}_2\%} = \frac{V}{\text{CO}_2}$  (or the ventilation equivalent [V.E.] for  $\text{CO}_2$ ). Since the concentration of carbon dioxide in inspired atmospheric air is so small (0.04 per cent), for practical purposes the concentrations of expired and produced carbon dioxide have the same significance. Therefore, the concentration of carbon dioxide in the expired air may be used as

a simple practical measure of the relation of respiration to the output of carbon dioxide. In this way abnormalities in respiration can be readily detected, regardless of the size or metabolic activity of the subject.

The concentration of carbon dioxide may be expressed as a percentage or as a partial pressure; the partial pressure in the expired air saturated with water vapor at 37 C. = (barometric pressure corrected — 47 mm. of mercury)  $\times$  CO<sub>2</sub> %.

In the 500 subjects used in the previous correlation the coefficient of variation for the percentage of carbon dioxide was found to be 7.437 per cent, while the coefficient for the partial pressure was 7.406 per cent. The partial pressure of carbon dioxide in the expired air appears to be slightly less variable. This is consistent with the concept that respiration is regulated by the pressure of the respiratory gases.<sup>16</sup> In these studies the carbon dioxide tension of the expired air has been chosen as the most suitable measure of the volume of respiration. It should be remembered that the partial pressure of carbon dioxide in the expired air varies inversely with the volume of respiration, and thus a fall in the partial pressure is indicative of an increase in the volume of respiration beyond that normally expected from the rate of carbon dioxide production.

#### AVERAGE NORMAL VALUES AND THE VARIATION WITH SEX AND AGE

This study is based on 2,021 consecutive determinations of basal metabolism in subjects from whom had been excluded all those known to have any abnormality affecting respiration and all those with definite hypothyroidism or hyperthyroidism. Obviously, it cannot be stated that all abnormal subjects have been excluded. The frequency distribution (fig. 5) of the concentration of carbon dioxide in the expired air of these 2,021 subjects shows a curve of the Gaussian, or normal, type. The mean values and the variability for the series are shown in table 2.

Figure 6 and table 3 show the trends for both sexes from the age of 5 to 65 years and over. For males beyond the age of 55 the results may not be significant because of the limited number of subjects. With great variation in age there is relatively little variation in the average partial pressure of carbon dioxide in the expired air. In females up to the age of 60 the range of the means is only 4.5 per cent; it is somewhat greater in the smaller series of males.

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16. Boycott, A. E., and Haldane, J. S.: The Effects of Low Atmospheric Pressures on Respiration, *J. Physiol.* **37**:355, 1908. Haldane and Priestley.<sup>14</sup>

In both sexes ventilation tends to increase slightly with advancing age. It is interesting that during the years of menstruation females consistently show a slightly greater ventilation proportionate to carbon dioxide production. This may be due to the lower blood pressure or to the lower hemoglobin values of women before the menopause or may be related to the presence of the female sex hormones. The percentage variation between the sexes is small, at its maximum only about 4 per cent. The conclusion of Knipping and Moncrieff<sup>7</sup> that the ventilation equivalent is apparently uninfluenced by sex and age is

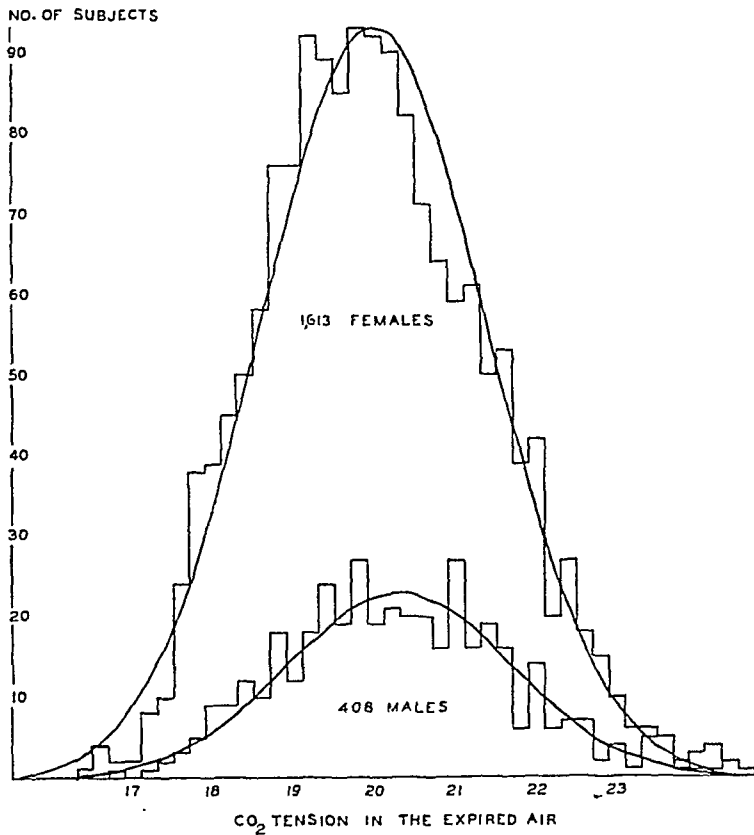


Fig. 5.—The carbon dioxide tension in the expired air in 2,021 subjects with known abnormality excluded. The calculated normal curve is superimposed.

TABLE 2.—Mean Values and Variability of the Concentration of Carbon Dioxide in Expired Air in 2,021 Subjects

Sex of Subjects	Number of Subjects	Mean CO <sub>2</sub> Tension	Standard Deviation	Coefficient of Variation, %
♀	1,613	20.01	1.38	6.93
♂	408	20.33	1.45	7.13

roughly and for practical purposes correct. The variations which do occur are interesting and significant, but for clinical purposes we

believe they are not sufficiently large to require the adoption of different normal standards for age and sex.

The average normal value for the concentration of carbon dioxide in the expired air as determined in our series is approximately 12 to 15 per cent lower than that calculated from the normal ventilation equivalents reported by other authors. This variance in results probably arises from differences in the type of apparatus and technic used. In this laboratory, when low resistance air valves were substituted for Sudd valves the concentration of carbon dioxide in the expired air was lowered about 10 per cent. We have also observed that the artificial introduction of obstruction in the apparatus tends to increase the concentration of carbon dioxide in the expired air. The use of a face mask rather than a mouth piece and nose clip is probably another

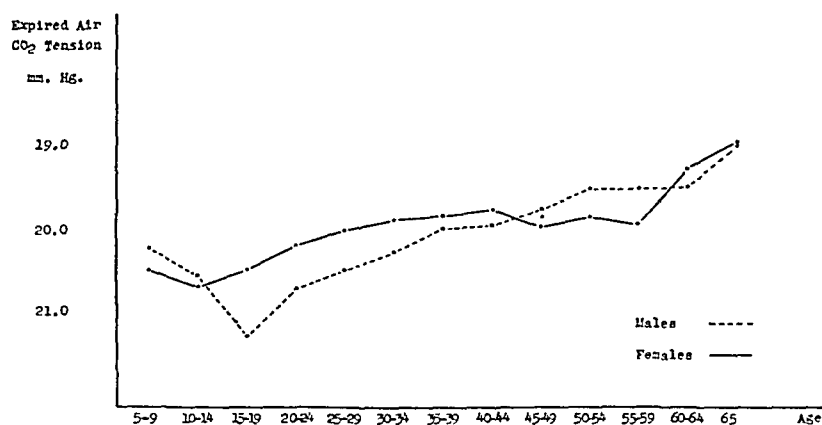


Fig. 6.—The relation of sex and age to the volume of respiration corrected for metabolic demand in 2,021 subjects with known abnormality excluded.

TABLE 3.—*Variation in the Concentration of Carbon Dioxide in Expired Air with Relation to Sex and Age*

Age, Yr.	Males		Females	
	Number of Subjects	Mean CO <sub>2</sub> Tension	Number of Subjects	Mean CO <sub>2</sub> Tension
5-9.....	21	20.23	48	20.48
10-14.....	100	20.56	89	20.69
15-19.....	36	21.34	138	20.51
20-24.....	32	20.72	169	20.21
25-29.....	36	20.48	223	20.02
30-34.....	53	20.27	213	19.87
35-39.....	42	19.97	207	19.84
40-44.....	27	19.94	161	19.75
45-49.....	27	19.76	156	19.98
50-54.....	17	19.51	108	19.84
55-59.....	5	19.51	59	19.94
60-64.....	5	19.47	32	19.25
65 and over.....	7	18.97	18	18.95

factor affecting the concentration. Higher concentrations may occur when subjects are not under basal conditions, and we do not know whether other investigations have always been made under basal metabolic conditions. Although absolute values may vary with the type of apparatus used, with uniform technic respiration can be accurately and consistently measured by means of the concentration of carbon dioxide in the expired air.

#### VARIABILITY OF THE TENSION OF CARBON DIOXIDE IN THE EXPIRED AIR

A preliminary survey of this question has been made according to the method used by Boothby and associates<sup>17</sup> in reporting the variability in basal metabolism. In physiologic measurements a certain variation may be found in a single subject examined several times in

TABLE 4.—*Variability of the Concentration of Carbon Dioxide in Expired Air*

	Coefficient of Variation	
	CO <sub>2</sub> Tension, %	Basal Metabolic Rate, %
Same subject, same day.....	1.6	3.0
Same subject, different days.....	2.7	4.1
Normal subjects.....	5.0	7.0*
Subject with known pathologic condition excluded.....	6.3	10.0*
All subjects, of various ages and both sexes, examined in one year.....	8.1	

\* Approximate.

any one day. When a single subject is examined on successive days a slightly greater variability is usually encountered. When measurements for different subjects are compared the variability is found to be greater, since one is now adding the difference existing between individuals. When normal subjects are examined the homogeneity of the group is the greatest and the variability the smallest.

In table 4 the coefficient of variation determined in our studies of the partial pressure of carbon dioxide in the expired air has been compared with the coefficient of variation of basal metabolic rates determined at the Mayo Clinic.<sup>17</sup> The variability for the same subject has been taken from previous records compiled for other purposes. The subjects were not all normal and frequently were under some type of treatment. The variability is therefore probably somewhat greater than could be obtained with untreated normal subjects. With a single trained subject the variability on the same and on successive days has been found to be

17. Boothby, W. M.; Berkson, J., and Plummer, W.: The Variability of Basal Metabolism: Some Observations Concerning Its Application in Conditions of Health and Disease, *Ann. Int. Med.* **11**:1014, 1938.

extremely small. The "normal" subjects included here comprise a small selected group in which history, physical examination, fluoroscopic or roentgenographic examination of the chest, or both, and electrocardiograms failed to reveal any abnormality. The group with known pathologic conditions excluded has been restricted to females under the age of 40.

Carpenter and Fox,<sup>18</sup> in commenting on the variability of the concentration of carbon dioxide in the expired air, stated:

In the course of experimental work of several years in which studies of expired air have been made, the narrowness of the range of the percentage of CO<sub>2</sub> of the expired air when the individual was at rest was one of the characteristic features. So nearly constant has it been in any single experiment, that we felt justified in searching for an error when this was not the case, and our judgment of other investigators' protocols is based upon this rule. When the conditions of the experiment are uniform, such as at rest without disturbing influence, drugs, or mechanical factors, we believe that the CO<sub>2</sub> per cent should be nearly constant on any single day.

We are in complete agreement with this view and believe that unless gross technical errors or varying conditions are introduced, the concentration of carbon dioxide in the expired air can be repeatedly obtained with a high degree of consistency.

If the variability of presumably normal subjects is considered to be approximately 5 per cent, practically all normal subjects will fall within a range of 10 per cent above and below the average normal. By the same reasoning, the normal variability of basal metabolism is confined to a range of 15 per cent above and below the average normal. It should be recognized that in making the normal range wide enough to include practically all normal subjects, a number of abnormal subjects are also included within these limits. As a preliminary working range of normal, approximately 10 per cent above and below an average normal has been chosen as most practical. If both sexes are included, the normal limits of the partial pressure of carbon dioxide in the expired air may be tentatively set at 18.00 to 22.50 mm. of mercury.

In studying the variation in the partial pressure of carbon dioxide in the expired air, it is important to consider the possible means by which the subject might purposely interfere with the test. The results of an experiment on the effects of voluntary hyperventilation are shown in table 5. In this experiment the respiratory exchange was first determined with normal quiet breathing. After this, the subject purposely

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18. Carpenter, T. M., and Fox, E. L.: The Effect of Muscular Work upon the Respiratory Exchange of Man After the Ingestion of Glucose and of Fructose, *Arbeitsphysiol.* 4:532, 1931.

overventilated as much as possible for four minutes, to an extent sufficient to produce marked subjective symptoms lasting several hours. The volume of ventilation was nearly trebled, but because of the large reserve of carbon dioxide present in the body, its elimination practically paralleled the increased breathing. Had overventilation been continued, the concentration of carbon dioxide in the expired air would have fallen still further as the reserves of carbon dioxide in the body became depleted. This has been observed in experiments on hyperventilation carried out over a longer period.<sup>19</sup> In our experiment, while other factors in the respiratory exchange were varied from 36 to 168 per cent, the pressure of carbon dioxide in the expired air was changed only 8.5 per cent by this extreme purposeful interference.

TABLE 5.—*Variation Produced by Deliberate Overventilation*

	Normal, Quiet Breathing (10 Min.)	Maximum Possible Overventilation (4 Min.)	Percentage Change
Expired CO <sub>2</sub> tension*.....	23.21	21.23	8.5
Expired CO <sub>2</sub> , %.....	3.28	3.00	8.5
Absorbed O <sub>2</sub> , %.....	4.01	2.03	49.5
Respiratory quotient.....	0.81	1.46	80.0
Minute ventilation, liters per min.....	6.89	18.49	168.5
CO <sub>2</sub> elimination, Cc. per min.....	223	547	145.0
O <sub>2</sub> absorption, cc. per min.....	276	375	36.0
Heat production, calories per hour.....	79.84	113.71	42.0
Basal metabolic rate, %.....	+2	+45	42.0
Tidal air, cc.....	449	1,216	168.5
Respiratory rate.....	15	15	....

\* This experiment was conducted one and three-quarters hours after the ingestion of food; the high partial pressure of carbon dioxide is due to the alkaline tide.

The striking constancy of the concentration of carbon dioxide is probably dependent on the fact that ventilation follows closely the production of carbon dioxide and even when ventilation is temporarily excessive elimination still tends to parallel ventilation because of the readily available reserve of carbon dioxide in the body. Thus the tension of carbon dioxide in the expired air in a ten minute test actually represents the relation of respiration and carbon dioxide production over a considerably longer period; this is not true in tests based on oxygen absorption.

Rapid, shallow breathing, such as is employed by the panting dog, markedly lowers the concentration of carbon dioxide in the expired air, without interfering with the normal ventilation of the lungs. In clinical examinations this type of breathing invalidates the test; its actual occurrence has been observed during the examination of hysterical

19. Soley, M. H., and Shock, N. W.: The Etiology of the Effort Syndrome, *Am. J. M. Sc.* **196**:840, 1938.



patients. In experiments conducted in this laboratory in which the respiratory rate was purposely varied over a wide range, the concentration of carbon dioxide in the expired air progressively decreased as the respiratory rate was increased. However, in tests carefully conducted under basal conditions such a type of respiration is rarely attempted and never permitted. The subject when relaxed and comfortable and left to his own choice does not select an exaggerated type of breathing.

#### RELATION OF THE CARBON DIOXIDE TENSION OF THE EXPIRED AIR TO THAT OF THE ALVEOLAR AIR

Under basal conditions the partial pressure of carbon dioxide in the expired air averages approximately 20.0 mm. of mercury, which is about half of the accepted tension of carbon dioxide in the alveolar air.<sup>14</sup> This is due to the fact that approximately half of the air expired comes from the alveoli of the lungs. In experiments in which the concentration of carbon dioxide was determined both in the alveolar air and in the expired air, Carpenter and Lee<sup>20</sup> found that the percentage in the expired air averaged consistently about 53 per cent of that in the alveolar air and that the alveolar carbon dioxide could be more accurately predicted by assuming that the dead space is a certain fraction of the tidal air and not a fixed volume. Physiologically the dead space in the respiratory tract varies with the depth of respiration, because gases pass through tubes, not as a piston displacement but rather as a spike or an axial stream,<sup>21</sup> and because of the rapid diffusion of gases.<sup>22</sup> Under basal metabolic conditions in this laboratory about half of the total volume of respiration is alveolar ventilation.

Wishfully thinking, one may prefer the measurement of alveolar ventilation; actually it is so difficult to obtain specimens of alveolar air even from trained subjects that its use in clinical medicine is of questionable value. On the other hand, the concentration of carbon dioxide in the expired air can be easily obtained; it is routinely determined in all basal metabolism examinations made with the open circuit type of apparatus. By using total ventilation instead of alveolar ventilation, studies of respiration can be made on large groups of normal subjects and subjects with pathologic conditions with a striking degree of accuracy.

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20. Carpenter, T. M., and Lee, R. C.: The Influence of Glucose and of Fructose on the Effective Dead Space in Human Respiration, *Am. J. Physiol.* **104**: 10, 1933.

21. Henderson, Y.; Chillingworth, F. P., and Whitney, J. L.: The Respiratory Dead Space, *Am. J. Physiol.* **38**:1, 1915.

22. Enghoff, H.: Zur Frage des schädlichen Raumes bei der Atmung. Eine statistische Studie, *Skandinav. Arch. f. Physiol.* **63**:15, 1932.

Clinically, the concentrations of carbon dioxide in the expired air and the alveolar air should both be regarded as measures of respiration. When respiration is unduly stimulated, both concentrations may be expected to fall. When respiration is depressed, both may be expected to rise. Without attempting to review the extensive literature on the alveolar carbon dioxide, we can state that some of the principal conditions in which one would expect undue stimulation of respiration, with a lowered concentration of carbon dioxide in the expired air, are inadequate circulation through the "respiratory center," deficient capacity of the blood to transport the respiratory gases (unless fully compensated by the circulatory system), retention of fixed acids in the blood and impairment in the gaseous exchange in the lungs. Thus, low concentrations of carbon dioxide in the expired air would be expected in persons with circulatory failure, severe anemia, "acidosis" and certain types of pulmonary disease. Respiratory depression and high concentrations of carbon dioxide in the expired air would be expected in persons with "alkalosis" and depression of the respiratory center, as caused by sleep and such drugs as morphine and the barbiturates.

#### SUMMARY

Respiration is carried out in order to obtain oxygen and to get rid of carbon dioxide. The volume of air breathed should be closely proportional to the volumes of oxygen needed and carbon dioxide produced.

In the study of a large group of subjects the correlation of ventilation both with oxygen consumption and with carbon dioxide production is excellent, but the correlation with carbon dioxide is better.

The ratio of ventilation and carbon dioxide output has been called the ventilation equivalent for carbon dioxide. The concentration of carbon dioxide in the expired air is the reciprocal of this ventilation equivalent; thus it is a means of measuring respiration adjusted for the rate of carbon dioxide production.

With the apparatus and technic used in this laboratory and under basal conditions, the average partial pressure of carbon dioxide in the expired air is about 20.0 mm. of mercury for females and 20.3 mm. for males. The average ventilation of females during the years of menstruation is consistently greater than that of males. The concentration of carbon dioxide in the expired air shows a slight tendency to fall with advancing age. The variation with age is small, and for clinical purposes a single standard is acceptable for both sexes and all ages.

In successive determinations both on the same subject and on large groups of subjects the variability is small. A range of 18.0 mm. to 22.5 mm. may be expected to include practically all normal subjects.

Clinically, low concentrations of carbon dioxide in the expired air (indicating undue respiratory stimulation) would be expected in subjects with circulatory failure, "acidosis," severe anemia and certain forms of pulmonary disease; high concentrations of carbon dioxide in the expired air (indicating respiratory depression) would be expected in persons with "alkalosis" and with depression of the respiration center, such as that caused by morphine or the barbiturates. Because of its simplicity and high degree of accuracy, this index of respiration can be used in physiologic and pathologic studies on large groups of subjects.

# ALKALOSIS COMPLICATING THE SIPPY TREATMENT OF PEPTIC ULCER

AN ANALYSIS OF ONE HUNDRED AND THIRTY-FIVE  
EPISODES

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The present investigation was undertaken in an effort to clarify further the problem of alkalosis and also to evaluate its relation to the kidney. For this purpose, an analysis has been made of 135 episodes of alkalosis observed by us during the alkali treatment of peptic ulcer. The study is of special interest in that in some cases renal function, as measured by the urea clearance test, was determined before, during and after the alkalosis.

## METHOD

Between 1929 and 1939 approximately 1,350 patients with peptic ulcer were treated at the Albert Merritt Billings Hospital by the Sippy program. This regimen included the frequent use of milk and cream and soft foods, nightly aspiration of the gastric contents and the hourly administration of alkali. The combinations of alkali used were (1) 0.6 Gm. of calcium carbonate and 2.0 Gm. of sodium bicarbonate, (2) 1.2 Gm. of calcium carbonate and 2.0 Gm. of sodium bicarbonate and (3) 2.0 Gm. of calcium carbonate and 2.0 Gm. of sodium bicarbonate. Six tenths of a gram each of magnesium oxide and sodium bicarbonate was employed to regulate bowel activity. Thirty-two grams of sodium bicarbonate and 10 to 32 Gm. of calcium carbonate thus was administered daily. The protein intake of these patients varied from 35 to 40 Gm. daily for the first few days; as feedings were added, the protein intake was increased rapidly to 65 Gm., and after two weeks it averaged 75 to 80 Gm. daily. Alkalosis, as indicated by an alteration in the acid-base balance, occurred in 135 episodes in 111 patients.<sup>1</sup> The series comprises 117 men and 18 women of ages ranging from 20 to 79. The high incidence of males follows the usual sex distribution of ulcer in our patients of about 6 to 1.

Determinations were made of the serum carbon dioxide,  $p_H$  and chloride and of the blood urea nitrogen at variable intervals during therapy.<sup>2</sup> Routine examina-

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1. For the purpose of clarity, the 135 instances of alkalosis will be referred to as 135 patients, since the multiple episodes of alkalosis in 18 patients each occurred during separate admissions to the hospital.

2. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931, vol. 2: Serum Carbon Dioxide, p. 283;  $p_H$  (Colorimetric), p. 796; Chloride, p. 835; Blood Urea Nitrogen, p. 367.

tions were made of the urine in all cases, and in addition, renal function was measured by the urea clearance test of Van Slyke and associates.<sup>3</sup> The urea clearance tests were carried out in the hospital and in the outpatient clinics. The analyses were made by trained laboratory assistants under the direction of a chemist, Dr. Kathryn Knowlton, but not by her directly, by ourselves or by research chemists. Nevertheless, we believe the determinations to be quite reliable and to constitute at least a satisfactory "first approximation." The urea clearance test is not an absolute measure of renal function. It may be influenced by various extrarenal factors, such as dehydration, a low output of urine and the protein content of the diet. Rather widely variable results have been noted in presumably normal subjects. However, the urea clearance test, when carefully performed, is probably superior to such tests as the phenolsulfonphthalein excretion and the sulfate clearance test.

Values of 75 per cent or more of average normal were considered normal; those between 55 and 75 per cent were arbitrarily classified as slightly reduced, while values below 55 per cent of average were accepted as definitely low. The results are presented chiefly as an indication of the trend of renal function in

TABLE 1.—*Acid-Base Balance During Alkalosis*

Degree of Alkalosis	Number of Patients	Sex		Avg. Age, Yr.	Serum Chloride, mM/L. Normal, 95=105		Serum CO <sub>2</sub> , mM/L. Normal, 22=30		Serum pH Normal, 7.35=7.45	
		♂	♀		Range	Avg.	Range	Avg.	Range	Avg.
Slight	71	58	13	43	85.4=102.5	95.0	31 =39.8	34.1	7.40=7.65	7.51
Moderate	27	25	2	47	80.0= 91.1	88.0	35.9=43.3	39.2	7.50=7.72	7.56
Severe	37	34	3	51	60.0= 90.4	77.0	38.6=62.1	48.0	7.52=7.73	7.61
Totals	135	117	18							

relation to alkalosis. No attempt is made to define the nature of the renal disturbance. This problem is now being investigated more fully with the inulin and the diodrast, as well as the urea, clearance test and will be the subject of a future report.

#### ACID-BASE BALANCE

Alkalosis is characterized chemically by an elevation in the serum carbon dioxide and  $p_H$  and frequently by a decrease in the serum chloride. In this study the degree of the acid-base disturbance was evaluated and classified on the basis of these alterations in the electrolyte balance. The clinical severity and course of each individual case was also appraised. As may be seen from table 1, slight alkalosis occurred in 71 patients, moderate alkalosis in 27 and severe alkalosis in 37. The range of serum chloride, carbon dioxide and  $p_H$  are noted in the table. We have not studied the relation of the individual changes to each

3. Van Slyke, D. D., and others: Observations on Courses of Different Types of Bright's Disease and on Resultant Changes in Renal Anatomy, *Medicine* 9:257 (Sept.) 1930.

other, as Hastings and Steinhaus<sup>4</sup> and Eisele<sup>5</sup> have done, but rather the relation between the total alteration in serum electrolytes and renal function as indicated by the urea clearance test.

## CLINICAL ASPECTS

The incidence of alkalosis according to age decades is shown in table 2. As was to be expected, most of the patients were between 30 and 60 years of age. It will be noted also that the incidence of moderate and severe alkalosis increased in the older age groups. Alkalosis appeared more than once in 18 patients (table 3), twice in each

TABLE 2.—*Age Incidence*

Age by Decades	Degree of Alkalosis		
	Slight	Moderate	Severe
20-29 yr. ....	12	2	3
30-39 yr. ....	16	5	8
40-49 yr. ....	16	9	7
50-59 yr. ....	17	6	6
60-69 yr. ....	10	5	10
70-79 yr. ....	....	....	3
Totals .....	71	27	37

TABLE 3.—*Multiple Episodes of Alkalosis*

No. of Patients	Avg. Age, Yr.	No. of Episodes		Urea Clearance Prior to Alkalosis				Degree of Alkalosis		
		Two	Three	Normal	Slightly Reduced	Low	Undetermined	Slight	Moderate	Severe
18	43	13	5	5	3	6	4	22	7	13

of 13 patients and three times in each of 5 patients. Renal function prior to this complication had been normal in 5 patients and slightly reduced or low in 9 (undetermined in 4). We have noted frequently that after recovery from alkalosis the administration of alkali may subsequently be resumed without difficulty and without chemical alkalosis. This phenomenon was observed in 29 patients of the present series (table 4). The ingestion of alkali was resumed without the development of symptoms by many more patients, but chemical studies were not made.

4. Hastings, A. B., and Steinhaus, A. H.: A New Chart for the Interpretation of Acid-Base Changes and Its Application to Exercise, *Am. J. Physiol.* **96**:538 (March) 1931.

5. Eisele, C. W.: Changes in Acid Base Balance During Alkali Treatment for Peptic Ulcer, *Arch. Int. Med.* **63**:1048 (June) 1939.

There were 4 deaths in this series attributable to the syndrome of alkalosis, hypochloremia and dehydration. In all cases there was persistent vomiting secondary to pyloric obstruction. The results of necropsy performed in the 4 cases are described elsewhere in connection with a study of the effects of prolonged alkali therapy on the structure of the kidney. The findings may be briefly summarized by the statement that there were no microscopically detectable alterations in the kidneys attributable to the alkalosis other than the presence in the collecting tubules of blue-staining crystalline material, probably representing calcium, in 3 of the 4 cases.

The symptoms of alkalosis usually appeared between the fourth and the tenth day of treatment, although in some patients not until after several weeks had elapsed. The earliest complaints were a distaste for milk and cream and alkali, followed by weakness, dizziness, headache, dryness of the mouth, nausea and vomiting. Nervousness, clouding of the mentality and changes in personality were occasionally observed; these

TABLE 4.—*Normal Acid-Base Balance in Twenty-Nine Patients\* During Alkali Therapy After One or More Episodes of Alkalosis*

No. of Patients	Average Age, Yr.	No. of Episodes			Degree of Previous Alkalosis		
		After One	After Two	After Three	Slight	Moderate	Severe
29 .....	40	24	4	1	13	7	9

\* Limited to those with available data on acid-base balance during subsequent alkali therapy.

manifestations progressed in a few instances to actual coma. Muscular twitchings and hyperactive reflexes were noted infrequently. Two patients described a persistent aching in the jaws and teeth, although no dental abnormality could be detected. Tetany and mild convulsions appeared in only 1 patient; the alkalosis in this patient had been intensified by persistent vomiting secondary to pyloric obstruction. These manifestations disappeared with varying rapidity after the administration of adequate quantities of sodium chloride and water. It should be noted that the majority of patients with slight alkalosis and several with moderate or severe alkalosis did not exhibit any symptoms, the condition being detected only by routine chemical determinations. There was not a direct relation between the severity of symptoms and the degree of alkalosis or between the quantity of alkali administered and the frequency of the condition. It occurred in a 29 year old man after the administration of 27 Gm. of calcium carbonate and 90 Gm. of sodium bicarbonate in three days, whereas the acid-base balance remained normal in a 25 year old man receiving the same daily dose for fifty-four days (total intake—654 Gm. of calcium carbonate and 1,620 Gm. of sodium bicarbonate).

## CONTRIBUTORY FACTORS

*Massive Hemorrhage.*—Jordan and Kiefer,<sup>6</sup> Bockus and Bank,<sup>7</sup> and Jeghers and Lerner<sup>8</sup> have suggested that massive hemorrhage may increase the tendency to alkalosis. It is of interest to note, therefore, that in the present series, hemorrhage had occurred in 60 of the 135 patients. The alkalosis was slight in 34 patients, moderate in 13 and severe in 13. On the other hand, the acid-base balance remained normal during alkali therapy in a group of 38 patients with hemorrhage not included in the present study. There was no direct correlation between the severity of the bleeding and the frequency of alkalosis.

*Hypochloremia.*—Recent studies<sup>9</sup> have emphasized the important role of hypochloremia in the development of alkalosis during antacid therapy. It has been shown, for example, that the addition of sodium chloride often corrects the acid-base balance despite the continuation of

TABLE 5.—*Occurrence of Alkalosis in Patients with Hemorrhage from Peptic Ulcer*

Degree of Alkalosis	Number of Patients	Sex		Average Age, Yr.	Degree of Hemorrhage		
		♂	♀		Slight	Moderate	Severe
None .....	38	28	10	38	3	9	26
Slight .....	34	30	4	44	7	9	18
Moderate . . .	13	11	2	48	2	3	8
Severe ...	13	10	3	49	0	1	12
Total .....	98	79	19	....	...	...	...

alkali therapy. Chloride deficiency in patients with ulcer may result from the low intake of salt, which averages 2 to 3 Gm. daily instead of the usual 10 to 12 Gm., from vomiting and also from the nightly aspiration of the gastric contents. The loss of chloride by the latter route is of particular significance in patients with gastric retention and is frequently associated with marked dehydration. Gastric retention, as evidenced by the nightly aspiration of 200 cc. or more of gastric contents, was present in 6 of the 71 patients with slight alkalosis (8.5 per cent), in 10 of the

6. Jordan, S. M., and Kiefer, E. M.: Factors Influencing Prognosis in the Medical Treatment of Duodenal Ulcer, *Am. J. Surg.* **15**:472 (March) 1932.

7. Bockus, H. L., and Bank, J.: Alkalosis and Duodenal Ulcer, *M. Clin. North America* **16**:143 (July) 1932.

8. Jeghers, H., and Lerner, H. H.: The Syndrome of Alkalosis Complicating the Treatment of Peptic Ulcer—Report of Cases with a Review of the Pathogenesis, Clinical Aspects, and Treatment, *New England J. Med.* **214**:1236 (June 18) 1936.

9. Kirsner, J. B., and Palmer, W. L.: The Role of Chlorides in Alkalosis Following the Administration of Calcium Carbonate, *J. A. M. A.* **116**:384 (Feb. 1) 1941.



27 patients with moderate alkalosis (37 per cent) and in 20 of the 37 patients with severe alkalosis (54 per cent). The importance of gastric retention is further indicated by the fact that it was present in 25 of the 55 patients of the present series in whom the blood urea nitrogen increased during alkalosis. The absence of alkalosis in many patients receiving alkali and consuming a salt-poor diet suggests that the development of hypochloremia may be determined by individual variations in the fluid balance and salt reserve of the body prior to treatment.

*Antecedent Renal Disease.*—Renal Function Before Alkalosis: Many writers<sup>10</sup> have noted a definite correlation between the incidence of alkalosis and the presence of renal disease, although few studies of renal function have been made prior to the acid-base disturbance. Eisele obtained suggestive evidence of preexisting renal damage (as shown by changes in the blood pressure, anemia, arteriosclerosis and prostatism) in 19 of 28 patients. Wilkinson and Jordan,<sup>11</sup> using the sulfate clearance test, noted precedent renal impairment in a large number of cases in which alkalosis later developed. Alkalosis, nevertheless, may appear in the absence of renal impairment<sup>12</sup> and often does not occur in persons with renal disease.<sup>13</sup> Gatewood, Gaebler, Muntwyler and Myers<sup>14</sup> and Cope<sup>15</sup> could find no evidence of antecedent renal disease in the majority of their patients.

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10. (a) Hardt, L. L., and Rivers, A. B.: Toxic Manifestations Following the Alkaline Treatment of Peptic Ulcer, *Arch. Int. Med.* **31**:171 (Feb.) 1923. (b) Ellis, A. W. M.: Disturbance of the Acid-Base Equilibrium of the Blood to the Alkaline Side: Alkalemia, *Quart. J. Med.* **17**:405 (July) 1924. (c) Berger, E. H., and Binger, M. W.: The Status of the Kidneys in Alkalosis, *J. A. M. A.* **104**:1383 (April 30) 1935. (d) Shattuck, H. F.; Rohdenburg, E. L., and Booher, L. E.: Antacids in the Medical Management of Peptic Ulcer, *ibid.* **82**:200 (Jan. 19) 1935. (e) Way, C. T., and Muntwyler, E.: Alkalosis: Clinical Problem, *Ann. Int. Med.* **8**:818 (Jan.) 1935.

11. Wilkinson, S. A., and Jordan, S. M.: The Significance of Alkalosis in the Treatment of Peptic Ulcer, *Am. J. Digest. Dis. & Nutrition* **1**:509 (Sept.) 1934.

12. (a) Wildman, H. A.: Chloride Metabolism and Alkalosis in the Alkali Treatment of Peptic Ulcer, *Arch. Int. Med.* **43**:615 (May) 1929. (b) Cooke, A. M.: Alkalosis Occurring in the Alkaline Treatment of Peptic Ulcer, *Quart. J. Med.* **1**:527 (Oct.) 1932. (c) Nicol, B. M.: The Renal Changes in Alkalosis, *ibid.* **9**:91 (Jan.) 1940.

13. (a) Jordan, S. M.: Calcium, Chloride, and Carbon Dioxide Content of Venous Blood in Cases of Gastro-Duodenal Ulcer Treated with Alkalis, *J. A. M. A.* **87**:1906 (Dec. 4) 1926. (b) Oakley, W. M.: Alkalosis Arising in the Treatment of Peptic Ulcer, *Lancet* **2**:187 (July 27) 1935. (c) Jeghers and Lerner.<sup>8</sup> (d) Berger and Binger.<sup>10c</sup> (e) Cooke.<sup>12b</sup>

14. Gatewood, W. E.; Gaebler, O. H.; Muntwyler, E., and Myers, V. C.: Alkalosis in Patients with Peptic Ulcer, *Arch. Int. Med.* **42**:79 (July) 1928.

15. Cope, C. L.: Base Changes in the Alkalosis Produced by the Treatment of Gastric Ulcer with Alkalis, *Clin. Sc.* **2**:287 (July) 1936.

In the present study, 16 episodes of alkalosis occurred in persons with disease of the genitourinary tract (table 6). Of these patients, nephrolithiasis was present in 5, ureteral calculus in 6, recent pyelitis in 2 and bilateral ascending suppurative nephritis, chronic nephritis and multiple urethral strictures in 1 each of the remaining 3. On the other hand, the acid-base balance was undisturbed in a group of 23 patients with similar conditions receiving alkali. This group comprised 10 patients with nephrolithiasis, 11 with ureteral calculus, and 1 each with a post-transfusional nephropathy and renal tuberculosis. The initial urea

TABLE 6.—*Occurrence of Alkalosis in Thirty-Nine Patients with Ulcer and Renal Disease*

	No. of Patients	Average Age, Yr.	Renal or Ureteral Calculus	Other Renal Disease	Urea Clearance Preceding Alkalosis			Degree of Alkalosis		
					Normal	Low	Undetermined	Slight	Moderate	Severe
Alkalosis	16	50	11	5	3	6	7	7	6	3
No alkalosis	23	42	21	2	10	6	7	..	..	..

TABLE 7.—*Occurrence of Alkalosis in Fifty-Four Patients with Ulcer and with Hypertension*

	No. of Patients	Average Age, Yr.	Urea Clearance Preceding Alkalosis			Degree of Alkalosis		
			Normal	Low	Undetermined	Slight	Moderate	Severe
Alkalosis	37	50	7	14	16	14	13	10
No alkalosis	17	53	7	8	2	...	...	...

clearance was normal in 3 of 9 patients with renal disease in whom alkalosis developed, as compared with normal clearances in 10 of 16 patients in whom alkalosis did not develop.

Thirty-seven of the 135 episodes of alkalosis occurred in patients with hypertension (table 7). The urea clearance at the onset of treatment had been normal in 7 patients and reduced or low in 14 of this group (undetermined in 16). We have used alkali therapy rather routinely for hypertensive patients with ulcer, but adequate electrolyte studies are available only for the 17 patients in whom symptoms of alkalosis did not develop. Renal function at the onset of treatment had been normal in 7 patients and low in 8 of this group (undetermined in 2).

The effect of alkalosis on the urea clearance was studied in 48 patients of the present series.<sup>16</sup> Renal function at the onset of alkali therapy was normal in 24 patients, reduced in 8 and low in 16 (table 8). A normal value for urea clearance was obtained prior to alkalosis in 12 of 23 patients with slight alkalosis, in 8 of 13 patients with moderate alkalosis and in 4 of 12 patients with severe alkalosis.

**Renal Function During Alkalosis:** Urea and sulfate clearances, as well as the excretion of phenolsulfonphthalein, have been found reduced during alkalosis by various workers.<sup>17</sup> The mechanisms by which the decrease is brought about and the nature of the renal lesion are not known. The latter apparently does not consist of a microscopically detectable morphologic alteration in the kidney.<sup>18</sup> McCance and Widdowson<sup>17a</sup> observed a fall in creatinine, sucrose, inulin and urea clearances in a patient with alkalosis resulting from pyloric obstruction and suggested that the major dysfunction was a decrease in glomerular

TABLE 8—*Urea Clearance in Forty-Eight Patients at the Beginning of Alkali Therapy*

Degree of Alkalosis	No. of Patients	Urea Clearance at Initiation of Alkali Therapy		
		Normal	Slightly Reduced	Low
Slight	23	12	3	8
Moderate	13	8	1	4
Severe	12	4	4	4
Total	48	24	8	16

filtration. The impaired renal function also has been related to dehydration with its attendant consequences.<sup>9</sup> In the present study the urea clearance was determined during alkalosis in the same 48 patients considered in the preceding paragraph (table 9). No change in renal function was noted in 20 patients. In 14 of these the original urea clearance had been normal. In the 28 instances in which renal function decreased, the change was arbitrarily considered as slight<sup>19</sup> in 4, mod-

16. Values for urea clearance were obtained at the initiation of alkali therapy in 25 additional cases; these data are omitted from the present discussion because renal function was not measured during the period of alkalosis.

17. (a) McCance, R. A., and Widdowson, E. M.: Alkalosis with Disordered Kidney Function, *Lancet* 2:247 (July 31) 1937. (b) Wilkinson and Jordan.<sup>11</sup>

18. Kirsner, J. B.: The Effect of the Prolonged Administration of Large Quantities of Sodium Bicarbonate on the Kidney of the Dog, *Arch. Path.* 32:76 (July) 1941.

19. A slight change was estimated as a reduction of 15 to 25 per cent of average normal; a moderate change, as a reduction of 25 to 45 per cent of average normal, and a marked change, as a reduction of 45 per cent or more. The change was considered as a decrease from normal to low levels or to an indicated decrease within range of lowered values for clearance.

erate in 11 and marked in 13. Renal function originally had been normal in 10 patients and reduced or low in 18 patients of this group. The urea clearance decreased most frequently during severe alkalosis and apparently more often in patients with antecedent impairment of renal function. Thus, a diminution occurred in 10 of 24 cases in which a normal value for urea clearance had previously been obtained, whereas a decrease occurred in 18 of 24 cases in which the initial value had been low.

Renal Function Shortly After Alkalosis: The status of renal function shortly after alkalosis seems to have been determined only occa-

TABLE 9.—*Urea Clearance in Forty-Eight Patients During Alkalosis*

Degree of Alkalosis	Urea Clearance Originally Normal (24 Patients)		Urea Clearance Originally Low (24 Patients)	
	Unchanged During Alkalosis	Decreased During Alkalosis	Unchanged During Alkalosis	Decreased During Alkalosis
Slight .....	7	5	4	7
Moderate .....	7	1	2	3
Severe .....	0	4	..	8
Total .....	14	10	6	18

TABLE 10.—*Urea Clearance Shortly After Alkalosis in Twenty-Two Patients in Whom a Decrease Had Been Observed During the Acid-Base Disturbance*

Subsequent Status	No. of Patients	Original Status of Urea Clearance		Degree of Alkalosis		
		Normal	Low	Slight	Moderate	Severe
Return to original level.....	19	6	13	9	2	8
Lower than original level.....	3	2	1	1	1	1
Total .....	22	8	14	10	3	9

sionally by other investigators. Jeghers and Lerner observed 1 case in which there was evidence of renal impairment four months after restoration of a normal acid-base balance. Berger and Binger noted decreased function in 5 of 7 patients several weeks after alkalosis. Binger, Hastings and Neill<sup>20</sup> administered 5.7 Gm. of sodium bicarbonate to a patient for thirty-five days; alkalosis resulted, but there was no evidence of damage to the kidneys other than a slightly reduced phthalein excretion. Cope reported the case of a man who had expe-

20. Binger, C. A. L.; Hastings, A. B., and Neill, J. M.: Edema Associated with Moderate Bicarbonate Administration During Convalescence from Pneumonia, *Arch. Int. Med.* **31**:145 (Jan.) 1923.

rienced four severe attacks of alkalosis; the urea clearance after recovery from the fourth episode was 92 per cent. Normal function after alkalosis has been reported also by Gatewood, by Cooke and by others.

In the present series, of 28 patients in whom, as mentioned previously, the urea clearance fell during alkalosis, further determinations were made on 22 within several weeks after the episode (table 10). The clearance returned to its previous level in 19 of the 22 patients shortly after alkalosis. The original values had been normal in 6 and reduced or low in 13 of this group. In the 3 patients in whom the clearance was below its initial level shortly after alkalosis, the original function had been normal in 2 and low in 1 (table 11). It should be noted that the urea clearance later returned to its original level in all 3 of these patients.

It is evident, therefore, that alkalosis does not cause a persistent diminution of renal function, although in occasional patients a decreased urea clearance may be demonstrable for at least several months.

**Blood Urea Nitrogen:** The blood urea nitrogen often rises markedly during alkalosis and returns to normal with recovery. The blood creatinine, inorganic phosphate and inorganic sulfate may do the same. In the present series, the blood urea nitrogen increased in 17 of the 71 patients with slight alkalosis (24 per cent), in 13 of the 27 patients with moderate alkalosis (48 per cent) and in 25 of the 37 patients with severe alkalosis (67.5 per cent) (table 12). The highest values for blood urea nitrogen occurred in patients in whom there was evidence of primary renal disease. The high incidence of other complications is of interest; hemorrhage was present in 16 patients, hypertension in 16 and gastric retention in 25. In this connection it should be emphasized that an elevation of the blood urea nitrogen does not per se indicate intrinsic renal disease.<sup>21</sup>

**Urine:** Although the presence of albumin, casts and red blood cells in the urine during alkalosis has been reported frequently,<sup>22</sup> this finding was uncommon in the present series. A trace of albumin was detected in the urine of 4 patients with slight alkalosis, in that of 7 with moderate alkalosis and in that of 10 with severe alkalosis. A moderate amount of albumin was found in the urine of 2 patients with moderate alkalosis. Hyaline and granular casts were noted in the urine of 1 patient with moderate alkalosis and in that of another with severe alkalosis. Both albumin and casts were present in the urine of 3 patients during severe alkalosis. Gross or microscopic hematuria was not observed.

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21. Kirsner, J. B., and Knowlton, K.: Acid Base Balance, Renal Function and Gastric Secretion During Hypochloremia in the Dog, *J. Clin. Investigation* 20:303 (May) 1941.

22. Jeghers and Lerner.<sup>8</sup> Hardt and Rivers.<sup>10a</sup> Jordan.<sup>13a</sup>

TABLE 11.—*Decreased Urea Clearance in Three Patients Shortly After Alkalosis*

Patient	Age, Yr.	Sex	Initial Urea Clearance, Percentage of Average Normal	Blood Urea Nitrogen, Mg./100 Cc.	Days After Alkalosis	Urea Clearance, After Alkalosis, Percentage of Average Normal	Blood Urea Nitrogen, Mg./100 Cc.	Comment	Subsequent Status of Urea Clearance
W. M.	36	♂	84	10.1	7	48	14.7	Hypertension	Returned to original level
C. G. R.	44	♂	102	17.4	6	58	16.3	Nephrolithiasis, gastric retention	Returned to original level
C. M.	54	♂	32=37	20.8=26.3	10	15	35.0	Moderate hypertension	Returned to original level

## TREATMENT

The treatment of alkalosis is simple and effective. It consists of the discontinuance of alkalis, the administration of either ammonium chloride or, preferably, sodium chloride in amounts varying from 5 to 15 Gm. daily and the administration of large amounts of water by mouth or by clysis. Fluids given parenterally, such as physiologic or 2 per cent solution of sodium chloride, may be necessary to combat the hypochloremia in the more severe forms of alkalosis. Although the

TABLE 12.—*Elevated Blood Urea Nitrogen During Alkalosis*

Blood Urea Nitrogen, Mg./100 Cc.	No. of Patients	Slight Alkalosis			Gastric Retention
		Associated Complications			
		Hemorrhage	Hypertension		
20- 30 .....	8	3	1		3
30- 40 .....	2	1	1		....
40- 50 .....	3	2	3		....
50-113.6 .....	4	3	3		....
Total .....	17	9	8		3
Moderate Alkalosis					
20-30 .....	8	1	2		3
30-40 .....	3	1	1		2
40-52.5 .....	2	1	....		....
Total .....	13	3	3		5
Severe Alkalosis					
20-30 .....	7	1	2		4
30-40 .....	8	2	2		5
40-50 .....	7	1	1		5
50-75 .....	3	....	....		3
Total .....	25	4	5		17
Grand total .....	55	16	16		25

use of a 5 per cent solution of dextrose in distilled water is of great value as supplemental therapy to relieve the dehydration, nevertheless physiologic solution of sodium chloride is to be preferred, for it replaces both the lost chloride and the water. The treatment of alkalosis in the present series is summarized in table 13.

Pyloric obstruction ultimately necessitating surgical intervention was present in the majority of patients requiring the parenteral administration of fluid. Clinical and chemical improvement rapidly ensued after the institution of these therapeutic measures; the acid-base balance usually was reestablished within two or three days after the parenteral use of fluid and within five to seven days in patients receiving sodium chloride and fluid by mouth.

EFFECT OF PROLONGED ALKALI THERAPY WITH AND WITHOUT  
ALKALOSIS ON RENAL FUNCTION

There have been few studies of renal function after prolonged alkali therapy. Gatewood and Myers<sup>23</sup> found no evidence of renal damage after the use of alkali in a series of 46 patients; the total intake of sodium bicarbonate, calcium carbonate and magnesium oxide averaged 30 Gm. daily. Gatewood and associates<sup>14</sup> reported similar results in another study in which renal function was estimated by the phenol-sulfonphthalein excretion test. Berger and Binger<sup>10c</sup> observed 1 patient who took massive quantities of sodium bicarbonate and calcium carbonate for many years without renal impairment developing. Steele<sup>24</sup> reported the case of a 52 year old man who had taken alkali for fourteen years. The urine contained albumin and casts; the blood urea nitrogen was elevated, and the ability of the kidneys to excrete urea and

TABLE 13.—*Treatment of One Hundred and Thirty-Five Episodes of Alkalosis*

Therapy	Degree of Alkalosis		
	Slight	Moderate	Severe
Alkali continued .....	46	5	0
Alkali stopped (no other treatment).....	12	6	5
Alkali changed .....	5	1	0
Alkali continued and NaCl or NH <sub>4</sub> Cl added.....	5	5	2
Alkali stopped and NaCl or NH <sub>4</sub> Cl added.....	1	6	18
Alkali stopped and fluids administered parenterally	2	4	12
Total .....	71	27	37

to concentrate urine was markedly reduced. The blood urea nitrogen returned to normal six months after alkali was discontinued, and the power of the kidneys to concentrate urine rose slowly to normal during a period of two years. Hyaline casts and red blood cells continued in the urine, and faint traces of albumin appeared occasionally. The interpretation of this case is somewhat difficult; the continued presence of hyaline casts, albumin and red blood cells suggests that preexistent renal disease may have been present and possibly further aggravated by the alkali. The concentrating and excretory powers of the kidney were eventually restored, thus indicating that no irreversible injury to the kidney had occurred.

The effect of prolonged alkali therapy on renal function has been studied by us in 62 patients (table 14). The patients may be divided

23. Gatewood, W. E., and Myers, V. C.: A Study of the Acid Base Balance of the Blood in Peptic Ulcer Cases Treated with Alkalis, *Tr. Am. Gastroenterol. A.*, 1927, p. 92.

24. Steele, J. M.: Renal Insufficiency Developing During Prolonged Use of Alkalis: Report of Case, *J. A. M. A.* **106**:2049 (June 13) 1936.



into two groups: (a) those without alkalosis at any time and (b) those in whom alkalosis occurred.<sup>25</sup>

Group (a) includes 29 patients, 25 males and 4 females, ranging in age from 26 to 65 years (average 44 years). Alkali had been used previously by 28 of this group. The initial value for urea clearance was normal in 18. The follow-up period varied from six to twelve months for two patients, from one to five years for 21 and from six to nine years for 6. During the period of observation varying quantities of alkali were taken by all 29 patients.

TABLE 14.—*Effect of Prolonged Alkali Therapy With and Without Alkalosis on Urea Clearance in Sixty-Two Patients*

	Therapy Uncomplicated By Alkalosis	Therapy Complicated By Alkalosis †	Total
Number of patients .....	29	33	62
Average age, yr.....	44	49	....
Initial Status of Urea Clearance			
Normal .....	18	14	32
Slightly reduced .....	7	11	18
Low .....	4	8	12
Final Status of Clearance			
Unimpaired .....	28	31	59
Lower than original .....	1	2	3
Amount of Alkali * Taken During Follow-Up Period			
Large .....	17	17	34
Moderate .....	9	12	21
Small .....	3	4	7

\* Large quantities were estimated as 40 to 60 Gm. daily; moderate quantities, 20 to 40 Gm. daily, and small quantities, 10 to 20 Gm. daily.

† 48 episodes of alkalosis.

The final urea clearance was unimpaired in 28 of the 29 patients. The only patient in whom the urea clearance seemed to be definitely lowered was a 68 year old woman in whom, after the ingestion of large quantities of alkali for five and one-half years, the urea clearance decreased from 67 to 40 per cent of average normal. The initial clearance of 67 per cent was obtained at a time when, on admission to the hospital, dehydration was present as a result of continued vomiting. The blood level of urea nitrogen was 36.2 mg. per hundred cubic centimeters. In the subsequent five and a half years the patient has taken large quantities of alkali and has remained well clinically. The urea clearance measures 40 per cent (two determinations, maximum clearances); the blood urea nitrogen is normal. There has been no elevation of the blood pressure. The urine does not contain albumin

25. The latter group is included in the series of patients already discussed.

or casts, and its specific gravity occasionally exceeds 1.020. Thus there is no conclusive evidence of renal injury in any of the 29 patients, even though 4 of them had pyloric stenosis, 2 had hypertension and 1 had a post-transfusional nephropathy.

These results indicate that prolonged alkali therapy uncomplicated by alkalosis does not impair renal function either in patients with normal urea clearance or in persons with preexisting renal impairment.

Group (b) consists of 33 patients, 27 males and 6 females, ranging in age from 25 to 71 (average 49 years), all of whom had taken alkali previously. The initial value for clearance was normal in 14 of these patients. The period of observation extended from two to twelve months for 6 patients, from one to five years for 19 and from five to ten years for 8. During this time varying amounts of alkali were used by 30 patients of the group. Alkalosis occurred on 48 occasions. According to the final test, urea clearance was unimpaired in 31 of the 33 patients. Renal disease was present in 6 patients of this group, gastric retention in 11 and hypertension in 6. A decrease in the urea clearance was observed in 2 patients, whose cases are reported in detail as follows:

CASE 1.—G. W., a 47 year old housewife, had experienced symptoms of ulcer for three and a half years. She had known for eight months that her blood pressure was elevated. The important physical findings on admission to the hospital were pallor of the skin, obesity and slight enlargement of the heart. The blood pressure was 150 systolic and 100 diastolic. Roentgen studies revealed a stenosing duodenal ulcer. One hundred and thirty-five grams of calcium carbonate and 450 Gm. of sodium bicarbonate was given in fifteen days (Feb. 28 to March 14, 1933). The acid-base balance remained normal; the urea clearance was 85 per cent of average normal, and the blood level of urea nitrogen was 7.9 mg. per hundred cubic centimeters. Moderate quantities of alkali were taken by the patient for the next seven months. She then reentered the hospital (October 10 to October 24) and received 96 Gm. of a mixture of sodium citrate and tribasic calcium phosphate in two days. The blood pressure was 178 systolic and 108 diastolic. Because of marked pyloric stenosis, a posterior gastroenterostomy was performed, from which the patient made an uneventful recovery. Small amounts of alkali were taken during the subsequent nine months, until July 23, 1934. The patient was then not seen again by us until May 15, 1936, at which time she was hospitalized because of a severe hemorrhage from a jejunal ulcer (May 15 to June 5). The blood pressure was 152 systolic and 90 diastolic. Seventy-eight grams of calcium carbonate and 160 Gm. of sodium bicarbonate was given in the first five days. Because of recurrent hematemesis, the alkali was discontinued for the next three days, during which time physiologic solution of sodium chloride was administered parenterally. Alkali therapy then was resumed, the patient receiving a total of 570 Gm. of the sodium citrate, tribasic calcium phosphate mixture in eleven days. There was no significant alteration in the acid-base balance; the blood level of urea nitrogen was 12.9 mg. per hundred cubic centimeters. Two months later the patient again entered the hospital, because of a recurrent massive hemorrhage (August 16 to October 11). The blood pressure was 160 systolic and 105 diastolic. Two blood transfusions were given, and on the fifth day the gastroenterostomy was taken down. Wangensteen aspiration was

required for eight days after operation; in addition to parenteral administration of fluids, therapy also included the use of the Winkelstein drip for eight days. Convalescence was complicated by the development of a coronary occlusion two weeks after the operation. The patient recovered, however, and received 90 Gm. of calcium carbonate and 330 Gm. of sodium bicarbonate. A moderately severe chemical alkalosis was noted on the twenty-eighth day of hospitalization, attributable possibly in part to the continued gastric aspiration. The urea clearance on the forty-fifth day of hospitalization was 40 per cent of average normal and the blood level of urea nitrogen 11.9 mg. per hundred cubic centimeters.

The fifth hospital admission occurred eight months later (April 15 to April 20, 1937) because of a recurrent duodenal ulcer. Alkali had been taken infrequently prior to hospitalization. The blood pressure at this time was 220 systolic and 135 diastolic. Forty-five grams of calcium carbonate and 150 Gm. of sodium bicarbonate was given in five days. The urea clearance on the second day measured 37 per cent and the blood level of urea nitrogen 32.0 mg. per hundred cubic centimeters; there was a slight chemical alkalosis at the time.

Five months later the patient was admitted for the sixth time (September 24 to October 12). The urea clearance one week previously had measured 52 per cent and the blood level of urea nitrogen 13.1 mg. per hundred cubic centimeters. The blood pressure was 180 systolic and 100 diastolic. Four hundred and twenty grams of calcium carbonate and 210 Gm. of sodium bicarbonate was given in nineteen days. Alkali therapy was complicated by a moderate chemical alkalosis, which subsided after the administration of 4.0 Gm. of ammonium chloride daily for five days. The urea clearance, after restoration of the acid-base balance, was 48 per cent of average normal and the blood level of urea nitrogen 11.3 mg. per hundred cubic centimeters. Roentgen irradiation (a total of 3,878 r) was directed to the fundus of the stomach through anterior and posterior portals for fourteen days in an effort to reduce gastric acidity. A histamine achlorhydria was noted several weeks later (October 29). Alkali therapy was discontinued at this time and was not resumed thereafter.

Two admissions to the hospital were required during the next four years because of attacks of biliary colic, which subsided without surgical intervention. The blood pressure varied from 140 to 218 systolic and from 90 to 128 diastolic. Seven and eight years after the initial visit urea clearances measured 70 and 67 per cent of average normal, respectively, and the values for blood urea nitrogen were 13.9 and 17.8 mg. per hundred cubic centimeters, respectively. On June 19, 1941, eight years and three months after the original hospital entry the final value for urea clearance was 61 per cent of average normal and the final values for blood urea nitrogen was 16.6 mg. per hundred cubic centimeters. No alkali had been taken for almost four years prior to this last determination.

CASE 2.—I. J. S., a 31 year old salesman, had experienced symptoms of ulcer for one month prior to admission to the hospital. Physical examination revealed nothing abnormal except for tenderness in the epigastrium; the blood pressure was 128 systolic and 80 diastolic. Roentgenograms revealed a stenosing duodenal ulcer. Three hundred and eighty-seven grams of calcium carbonate and 720 Gm. of sodium bicarbonate was administered in twenty-four days (May 9 to June 31, 1931). The urea clearance on the third day of hospitalization was 99 per cent of average normal and the blood level of urea nitrogen 9.6 mg. per hundred cubic centimeters. A moderately severe alkalosis was detected on the fifteenth day of hospitalization. The urea clearance at this time was 78 per cent and the blood level of urea nitrogen 10.9 mg. per hundred cubic centimeters. After recovery

from the alkalosis, the patient was observed in the outpatient department for six months; alkali was taken infrequently. The patient was then not seen by us for one year.

He reentered the hospital on Oct. 10, 1933, because of a massive hemorrhage. Physical examination disclosed severe hypertension; the blood pressure varied from 180 to 200 systolic and from 100 to 114 diastolic. One hundred and fifty grams each of calcium carbonate and sodium bicarbonate was given in the first five days. A severe alkalosis was detected at this time, and the alkali was discontinued. After restoration of the acid-base balance, the urea clearance increased from 41 to 63 per cent and the blood level of urea nitrogen, which had risen to 28.4 mg. per hundred cubic centimeters, decreased to 13.8 mg. per hundred cubic centimeters. Six examinations of the urine yielded negative results. Two months later the urea clearance measured 80 per cent of average normal and the blood urea nitrogen 13.9 mg. per hundred cubic centimeters. Alkali was taken infrequently in the subsequent five months. The hypertension persisted with readings in the neighborhood of 185 systolic and 120 diastolic.

Hospitalization again was necessary on March 19, 1934, because of sudden blurring of vision which had progressed to almost complete blindness. Physical examination revealed a definite hemianalgesia; the blood pressure was 230 systolic and 120 diastolic. Involuntary movements and jacksonian convulsions developed, and the patient lapsed into a coma which persisted for several days. There was subsequently a rapid improvement, both in mental clearness and in vision. No alkali was administered during this period of hospitalization. Small quantities of a mixture of sodium citrate and tribasic calcium phosphate were taken daily during the next two and one-half years. The blood pressure fluctuated from 150 to 196 systolic and from 96 to 130 diastolic.

The patient entered the hospital a fourth time, on May 24, 1937, because of recurrent bleeding. Four hundred and eighty grams of the sodium citrate, tribasic calcium phosphate mixture and 1,020 Gm. of the same combination of alkalis with 10 per cent ammonium chloride added was given in twenty-five days (May 24 to June 18). The urea clearance on three occasions measured 23, 29 and 29 per cent and the blood level of urea nitrogen varied from 19.5 to 26.0 mg. per hundred cubic centimeters. Roentgen irradiation (a total of 3,050 r) was directed to the fundus of the stomach through anterior and posterior portals for ten days in an effort to reduce gastric acidity. The irradiation produced a histamine achlorhydria, which persisted for several months. During the subsequent twelve months the patient took no alkali. His blood pressure fluctuated from 146 to 156 systolic and from 80 to 98 diastolic. Occasional specimens of urine contained slight to moderate amounts of albumin. The specific gravity varied from 1.010 to 1.026. On June 8, 1938, seven years after the initial determinations, the final value for urea clearance was 45 per cent of average normal and the blood level of urea nitrogen was 28.6 mg. per hundred cubic centimeters.

It will be noted that both patients had received comparatively small quantities of alkali. Indeed, none had been taken for long intervals during the period of observation. In the first case the clearances of 67 and 61 per cent actually represent good renal function in view of the hypertension and the numerous additional complications. In the second case the appearance of hypertension two years after the initial visit is, we think, unrelated to the alkali therapy. The possibility that the alkali contributed to the impairment of renal function cannot be definitely

excluded, but, in our opinion, the decreased urea clearances are attributable entirely to the hypertension and to associated renal arteriosclerosis.

It is clearly evident from this study, therefore, that prolonged alkali therapy, even though complicated by alkalosis, does not permanently depress the urea clearance, regardless of the original status of renal function.

#### SUMMARY

Alkalosis, as indicated by electrolyte changes in the serum, occurred on 135 occasions in 111 patients with peptic ulcer treated by the Sippy program. Multiple episodes of alkalosis occurred in 18 patients. The disturbance was slight in 71 instances, moderate in 27 and severe in 37. The electrolyte balance was undisturbed during subsequent alkali therapy in 29 persons who had recovered from a previous episode of alkalosis. The alkalosis was not a direct function of the quantity of alkali received. Symptoms usually appeared within four to ten days after the onset of treatment and consisted of a distaste for milk and cream, weakness, dizziness, headache, dryness of the mouth, nausea and vomiting. Many patients with slight alkalosis and several with moderate or severe alkalosis did not complain of any discomfort. There was no constant relation between the severity of symptoms and the degree of chemical alkalosis.

Bleeding occurred in 60 of the 135 episodes of alkalosis. There seemed to be no correlation between the severity of bleeding and the frequency of alkalosis. Gastric retention was present in 6 of 71 patients with slight alkalosis, in 10 of 27 patients with moderate alkalosis and in 20 of 37 patients with severe alkalosis.

Disease of the genitourinary tract was demonstrated in 16 patients. The urea clearance had been normal in 3 and reduced or low in 6 of this group. The acid-base balance was undisturbed in a group of 23 patients with renal disease similarly treated, in 10 of whom renal function at the onset of treatment had been normal and in 6 of whom it had been low. Thirty-seven of the 135 episodes of alkalosis occurred in patients with hypertension. The urea clearance previously had been normal in 7 and low in 14 of this group. Alkalosis did not occur in a group of 17 hypertensive patients with ulcer similarly treated, in 7 of whom renal function at the onset of treatment had been normal and in 8 of whom it had been low.

The effect of alkalosis on the urea clearance was studied in 48 patients of the present series. Renal function at the onset of alkali therapy was normal in 24 and reduced or low in 24. The urea clearance during alkalosis did not change in 20 patients, in 14 of whom normal values had been obtained originally. Renal function diminished in 28 patients; it previously had been normal in 10 and low in 18 of this group. The depression of the urea clearance during alkalosis

depended apparently on two factors (*a*) the severity of the alkalosis and (*b*) preexistent impairment of renal function.

The urea clearance was determined within several weeks after alkalosis in 22 of the 28 patients in whom it had decreased during the acid-base disturbance. A return to the previous level was noted in 19 patients; the original value had been normal in 6 of these and low in 13. Failure to return to the previous level was observed in 3 patients; the original values had been normal in 2 of these and low in 1. The urea clearance later returned to its original level in all 3 patients.

The blood urea nitrogen was elevated during alkalosis in 55 instances. Hypertension was present in 16 patients of this group, massive hemorrhage in 16 and gastric retention in 25. Albumin and casts were detected in the urine during alkalosis in 28 instances. Gross or microscopic hematuria was not observed.

It was not necessary to discontinue alkali for or to administer additional chloride to 51 of the 135 patients. Treatment of the remaining patients consisted variously of a change of antacid, the administration of either ammonium or sodium chloride, with or without the discontinuance of alkali, and the parenteral use of fluids. Clinical improvement rather rapidly followed the institution of these therapeutic measures.

The effect of prolonged alkali therapy on renal function was studied in 62 patients divided into the two following groups: (*a*) those whose condition was uncomplicated by alkalosis and (*b*) those in whom alkalosis developed. In group (*a*) there were 29 patients. The urea clearance decreased in only 1 of this group, diminishing from 67 to 40 per cent in a 68 year old woman after the ingestion of large quantities of alkali for five and a half years. The blood pressure, the value for blood urea nitrogen and the urine remained normal, however. In group (*b*) there were 33 patients among whom alkalosis occurred on 48 occasions. A decrease in the urea clearance was noted in only 2 patients of this group, each of whom had hypertension.

#### CONCLUSIONS

1. Alkalosis is a not infrequent complication of the Sippy treatment of peptic ulcer, although it may not be accompanied by clinical symptoms.

2. Alkalosis may develop in patients with normal renal function. The incidence of alkalosis is apparently greater in the presence of massive hemorrhage, after the loss of gastric juice either by vomiting or by therapeutic aspiration and in the presence of preexisting impairment of renal function.

3. The depression in renal function noted during alkalosis is usually temporary, although in occasional patients the decrease may persist for several months.

4. Renal function, as indicated by the urea clearance test, is not permanently decreased by the prolonged administration of alkali.

# PERIPHERAL BLOOD FLOW IN MYXEDEMA

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AND

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The cardiac output,<sup>1</sup> the circulating blood volume,<sup>2</sup> the velocity of blood flow, the pulse rate, the pulse pressure and the vital capacity<sup>3</sup> are decreased when the basal metabolic rate<sup>4</sup> is low in patients with myxedema. The pale, cold, dry skin of patients suffering from this disease suggested that there might be alterations of peripheral blood flow. Objective measurements, however, are not contained in the literature relating to the amount of blood allocated to the periphery. Stewart and Evans<sup>5</sup> found that the peripheral blood flow in patients with hyperthyroidism was increased and that it fell with the administration of iodine and decreased further still after subtotal thyroidectomy, so that there was a linear relation between basal metabolic rate and peripheral blood flow. The increase in peripheral blood flow accounted for the pink, moist skin which these patients exhibited. It was of interest to measure the peripheral blood flow, therefore, in patients with myxedema, at the other end of the metabolic scale from persons with hyperthyroidism. Data on such patients have now been accumulated and form the subject of this report. Six women suffering from myxedema were

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TABLE 1.—Data Relating to Six Patients Exhibiting Myxedema

Patient; Age, Yr.; Sex; Diagnosis	Date	Height, Cm.	Weight, Kg.	Total Surface Area, Sq. M.	Total Heat Production,* Cal. per Hr.	Average Room Temperature, C.	Average Rectal Temperature, C.	Average Skin Temperature, C.	Average Hand Temperature, C.	Average Foot Temperature, C.	Basal Meta- bolic Rate, %	Periph- eral Blood Flow, Cc. per Min.	Circu- lation Time (Sodium Dehydro- cholate), Sec.	Pulse Rate, per Min.	Pulse Pres- sure, mm. Hg.	Thyroid Therapy, Gm. Daily
L. C.; 60; ♀; spon- taneous myxedema	2/ 6/40	153.5	78.0	1.78	41.2	27.6	36.79	33.76	33.2	32.2	-30	14	14.9	60	22	None
	3/ 2/40	155.5	76.5	1.77	47.1	27.5	36.96	33.78	31.3	33.8	-18	49	12.8	73	34	0.012
	3/30/40	153.5	71.8	1.72	65.2	27.7	37.16	31.61	31.1	35.1	+16	137	11.5	90	30	0.060
	1/10/41	155.5	71.7	1.72	52.6	27.5	36.82	31.17	31.2	33.8	-4	91	11.2	74	54	0.075
E. S.; 32; ♀; spon- taneous myxedema	2/13/40	167.5	63.1	1.71	40.1	25.6	37.31	33.10	32.3	26.9	-34	22	21.8	49	20	None
	4/ 5/40	167.5	63.4	1.71	43.4	25.8	37.19	33.89	31.6	31.6	-29	61	20.1	48	30	0.045
	5/14/40	167.5	61.7	1.70	48.6	26.1	37.41	33.83	35.1	32.6	-19	71	12.5	59	36	0.120
	1/13/41	167.5	59.4	1.69	62.5	25.9	36.74	32.72	32.7	28.0	+ 5	92	10.9	60	34	0.210
M. P.; 30; ♀; spon- taneous myxedema	1/ 6/41	170.0	63.4	1.71	49.8	26.0	36.91	33.24	28.8	31.4	-20	10	12.9	60	24	None
	3/29/41	170.0	61.1	1.72	58.8	26.2	36.92	33.80	29.8	32.5	- 6	78	12.2	68	36	0.060
	4/19/41	170.0	60.8	1.71	60.0	26.0	36.56	33.18	32.9	33.1	- 2	79	12.3	64	32	0.120
	11/ 7/40	161.5	85.8	1.91	50.8	25.0	36.36	31.74	31.7	27.5	-26	7	19.6	60	12	0.015
R. M.; 30; ♀; spon- taneous myxedema	1/11/41	161.5	84.1	1.88	58.6	25.2	36.74	33.12	33.5	32.2	-13	55	16.6	64	26	0.030
	4/26/41	161.5	85.1	1.89	67.6	25.1	37.23	33.58	33.2	32.6	0	90	15.0	61	24	0.120
	11/ 6/40	147.0	66.8	1.60	32.8	25.2	36.87	32.19	31.1	27.2	-43	33	17.0	67	20	None
	1/ 2/41	147.0	66.7	1.60	53.4	25.5	37.31	34.14	31.4	29.8	- 7	68	14.9	66	30	0.030
M. K.; 39; ♀; postop- erative myxedema	2/14/41	147.0	68.3	1.61	58.6	25.1	36.86	33.97	34.0	30.3	+ 2	87	12.4	61	30	0.150
	1/16/41	172.0	67.4	1.82	43.7	25.0	36.90	32.96	31.2	23.5	-33	9	19.5	68	66	None
	2/ 3/41	172.0	67.5	1.83	62.7	25.2	37.25	34.21	35.2	26.4	- 7	71	15.1	72	50	0.060
	3/ 4/41	172.0	67.5	1.83	68.0	25.3	37.28	34.29	34.2	31.9	- 3	81	14.0	68	46	0.150

\* Calculated from oxygen consumption.<sup>5</sup>† Calculated by weighting the eleven individual skin temperatures according to the surface area represented by each.<sup>5</sup>



observed. All exhibited normal sinus mechanisms and were without signs and symptoms of congestive heart failure. Four of them (E. S., L. C., M. P. and R. M.) suffered from spontaneous myxedema and 2 (M. K. and E. B.) from postoperative myxedema (table 1).

#### METHOD

The peripheral blood flow was measured by the method employed by Stewart and Jack<sup>6</sup> and Stewart and Evans<sup>5</sup> in other investigations. The historical background of the method employed was discussed in their papers. In the description of the method in these papers the terminology of Winslow, Herrington and Gagge<sup>7</sup> relating to heat storage was used. After a recent informal discussion by Du Bois<sup>8</sup> with Burton and Gagge about this point it seemed best to make the terminology conform to that in most common usage, in that when there is a gain of heat to the body, or heat storage, it is called heat storage or "positive" heat storage. The formulas relating to heat storage used in the earlier papers<sup>9</sup> are now altered with this in view.

The equation used by Hardy and Soderstrom<sup>10</sup> for calculating peripheral blood flow is shown in formula I.

$$\text{Formula I. } F = 17 \times A \left( \frac{HI}{MR - MS} - \overset{\hat{\bullet}}{9.1} \text{ or } \overset{\bullet}{6.5} \right)$$

in which

$F$  = peripheral conductance above the minimal value

17 = factor for converting cal./C./M<sup>2</sup>/hr. into cc./min.

$A$  = surface area in sq. M.

$HI$  = heat loss (see formula II)

$MR$  = mean of rectal temperature

$MS$  = mean of the average skin temperature (derived by weighting)

9.1 = kilocal./C./M<sup>2</sup>/hr. (average thermal conductivity of superficial tissue with minimal blood flow for males in temperatures below 28 C.)

6.5 = same as the preceding equivalent but for females

$F$  in this formula measures the heat carried to the surface in excess of the heat conducted by the tissues. If blood enters the periphery at rectal temperature and finally reaches the surface at skin temperature,  $F$  will measure this flow in cubic centimeters per minute.

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6. Stewart, H. J., and Jack, N. B.: The Effect of Aminophyllin on Peripheral Blood Flow, *Am. Heart J.* **20**:205, 1940.

7. Winslow, C.-E. A.; Herrington, L. P., and Gagge, A. P.: Physiological Reactions of the Human Body to Varying Environmental Temperatures and Humidities, *Am. J. Physiol.* **120**:1, 1937.

8. Du Bois, E. F.: Personal communication to the authors.

9. Stewart and Evans.<sup>5</sup> Stewart and Jack.<sup>6</sup>

10. Hardy, J. D., and Soderstrom, G. F.: Heat Loss from the Nude Body and Peripheral Blood Flow at Temperature of 22 C. to 35 C., *J. Nutrition* **16**:493, 1938.

In the Hardy and Soderstrom<sup>10</sup> formula, heat loss was measured in a calorimeter. In the modification used by Stewart and Jack<sup>6</sup> and Stewart and Evans,<sup>5</sup> heat loss was calculated indirectly as follows:

Formula II.  $Hl = (Hp) - (Hs)$

The heat produced ( $Hp$ ) was derived by measuring oxygen consumption.

Heat storage ( $Hs$ ) could also be calculated, since data relating to changes in skin and in rectal temperature could be collected and substituted in formula III.

Formula III.  $Hs = W \times 0.8 [(\Delta R \times 0.8) + (\Delta S \times 0.2)]$

in which

$Hs$  = heat storage (final calculation on the basis of the cal./M<sup>2</sup>/hr.)

$W$  = body weight in Kg.

$0.8$  = average specific heat of body tissues

$\Delta R \times 0.8$  = weighted change in rectal temperature

$\Delta S \times 0.2$  = weighted change in average skin temperature

The changes in rectal temperature ( $\Delta R$ ) and in average skin temperature ( $\Delta S$ ) are expressed by formulas IV and V, respectively, as follows:

Formula IV.  $\Delta R = R_E - R_B$

in which

$\Delta R$  = change in rectal temperature

$R_E$  = rectal temperature at end of 20 minute period

$R_B$  = rectal temperature at beginning of 20 minute period

Formula V.  $\Delta S = S_E - S_B$

in which

$\Delta S$  = change in average skin temperature

$S_E$  = average skin temperature at end of 20 minute period

$S_B$  = average skin temperature at beginning of 20 minute period

Use of these formulas implies making a series of readings of skin and of rectal temperature at a known time and repeating the readings after a known interval. Twenty minute intervals were found to be satisfactory. Skin temperatures were taken at eleven points on the anterior surface of the body.<sup>9</sup> The average skin temperature was derived by weighting the temperatures of these eleven areas according to the amount of body surface represented by each (Hardy, Du Bois and Soderstrom<sup>11</sup>).

By substituting the data derived from formulas IV and V in formula III heat storage ( $Hs$ ) for known periods was calculated. After heat storage ( $Hs$ ) was calculated for a given interval, it was only necessary to subtract this from the heat produced ( $Hp$ ) in order to derive the heat loss ( $Hl$ ) for this period. By substituting the value for heat loss ( $Hl$ ) in formula I the peripheral blood flow was measured

11. Hardy, J. D.; Du Bois, E. F., and Soderstrom, G. F.: The Technique of Measuring Radiation and Convection, J. Nutrition **15**:461, 1938.

TABLE 2.—Data Relating to Patient L. C.

Age, Yr., and Sex	Height, Cm.	Weight (W), Kg.	Total Surface Area, (A), Sq. M.	Total Heat Pro- duction (HP),* Cal./Hr.	Basal Metabolic Rate, %	Time, a. m.	Room Temper- ature C.	Rectal Temper- ature (R), <sup>†</sup> F.	Average Skin Temper- ature (S), <sup>†</sup> F.	Skin Temperature (T), <sup>†</sup> of 11 Areas (Fig. 1), C.										
										T <sub>1</sub>	T <sub>2</sub>	T <sub>3</sub>	T <sub>4</sub>	T <sub>5</sub>	T <sub>6</sub>	T <sub>7</sub>	T <sub>8</sub>	T <sub>9</sub>	T <sub>10</sub>	T <sub>11</sub>
60; ♀	155.5	71.7	1.72	52.6	-4	10:05	27.6	36.84 = R <sub>n</sub>	34.30 = S <sub>B</sub>	34.5	34.7	35.4	34.5	34.3	34.2	34.2	34.4	33.6	33.5	33.5
						10:25	27.5	36.87 = R <sub>E</sub>	34.23 = S <sub>E</sub>	34.1	34.5	35.4	34.5	34.4	34.4	34.3	34.1	33.4	33.3	33.6

\* Calculated from oxygen consumption.<sup>5</sup>

† The inferior B indicates the temperature at the beginning of a twenty minute interval, and the inferior E indicates the temperature at the end of the interval.

‡ Measured with a radiometer.

for the known period in cubic centimeters per minute. Since the surface area of the body was known, blood flow was calculated as cubic centimeters per square meter per minute.

## EXAMPLE OF CALCULATION

In table 2 are recorded data concerning subject L. C. for the last twenty minute period shown in figure 1. By substituting these data in the appropriate aforementioned formulas the peripheral blood flow was calculated.

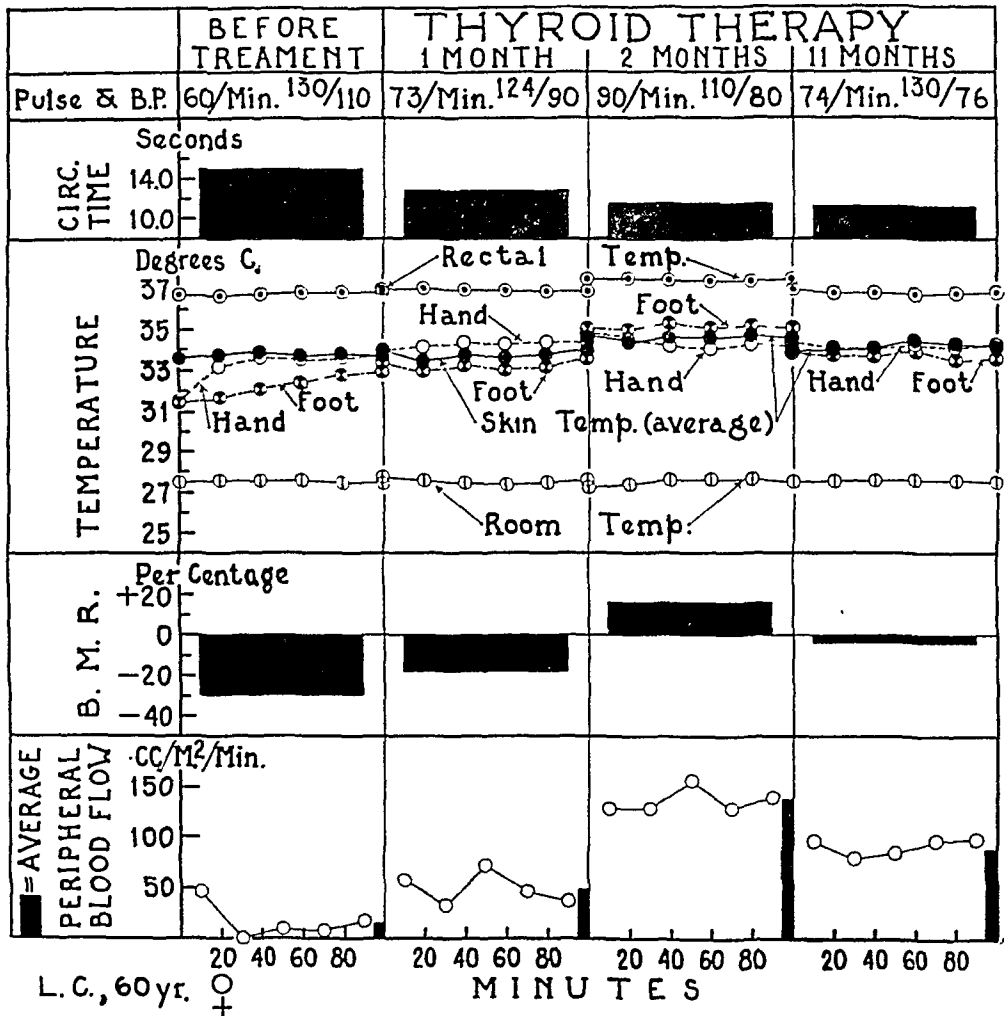


Fig. 1.—Data on patient L. C.

The average skin temperature ( $S$ ) was derived by weighting the skin temperatures ( $T$ ) of the eleven areas according to the percentage of surface area each represented.<sup>11</sup> The average skin temperature at the beginning ( $S_B$ ) of the last twenty minute period was calculated in the following manner:

$$\begin{aligned}
 S_B &= \left[ (T_1 \times 0.07) + \frac{(T_2 + T_3 + T_4)}{3} \times 0.35 + \frac{(T_5 + T_6)}{2} \times 0.14 + \right. \\
 &\quad \left. (T_7 \times 0.05) + \frac{(T_8 + T_9)}{2} \times 0.19 + (T_{10} \times 0.13) + (T_{11} \times 0.07) \right] \\
 &= \left[ (34.5 \times 0.07) + \frac{(34.7 + 35.4 + 34.5)}{3} \times 0.35 + \frac{(34.3 + 34.2)}{2} \right. \\
 &\quad \times 0.14 + (34.2 \times 0.05) + \frac{(34.4 + 33.6)}{2} \times 0.19 + (33.5 \times 0.13) \\
 &\quad \left. + (33.5 \times 0.07) \right] \\
 &= 34.30 \text{ C.}
 \end{aligned}$$

The average skin temperature at the end ( $S_E$ ) of the twenty minute period, calculated in a similar manner, was 34.23 C.

The rectal temperatures at the beginning ( $R_B$ ) and the end ( $R_E$ ) of the same twenty minute period were 36.84 C. and 36.87 C., respectively (table 2).

Therefore, the changes in temperature are calculated by substituting in formulas IV and V as follows:

$$\begin{aligned}\text{Formula IV: } \Delta R &= R_E - R_B \\ &= 36.87 - 36.84 \\ &= +0.03 \text{ C.}\end{aligned}$$

$$\begin{aligned}\text{Formula V: } \Delta S &= S_E - S_B \\ &= 34.23 - 34.30 \\ &= -0.07 \text{ C.}\end{aligned}$$

To calculate heat storage, substitute the values derived by formulas IV and V in formula III.

$$\begin{aligned}H_s &= W \times 0.8 [(\Delta R \times 0.8) + (\Delta S \times 0.2)] \\ &= 71.7 \times 0.8 [(+0.03 \times 0.8) + (-0.07 \times 0.2)] \\ &= 57.4 (+0.01) \\ &= +0.57 \text{ cal./20 min.}\end{aligned}$$

Since +0.57 cal. was the heat storage ( $H_s$ ) for a twenty minute period, the heat storage for an hour was derived by multiplying by 3.

$$\begin{aligned}H_s &= 3 \times +0.57 \text{ cal.} \\ &= +1.7 \text{ cal./hr.}\end{aligned}$$

Substitute in formula II.

$$\begin{aligned}H_l &= (H_p) - (H_s) \\ &= (52.6) - (+1.7) \\ &= 52.6 - 1.7 \\ &= 50.9 \text{ cal./hr.}\end{aligned}$$

To reduce heat loss to calories per square meter per hour, divide by surface area ( $A$ ), 1.72 sq. M.

$$\begin{aligned}H_l &= \frac{50.9}{1.72} \\ &= 29.6 \text{ cal./sq. M./hr.}\end{aligned}$$

The mean rectal temperature and the mean of the average skin temperature ( $MR$  and  $MS$ , respectively, in formula I) for the period were calculated as follows:

$$\begin{aligned}\text{Formula VI. } MR &= \frac{R_B + R_E}{2} \\ &= \frac{36.84 + 36.87}{2} \\ &= 36.86 \text{ C.}\end{aligned}$$

$$\begin{aligned}\text{Formula VII. } MS &= \frac{S_B + S_E}{2} \\ &= \frac{34.30 + 34.23}{2} \\ &= 34.27 \text{ C.}\end{aligned}$$

As the final step, substitute the values for heat loss ( $H_l$ ), the mean rectal temperature ( $MR$ ) and the mean of the average skin temperature ( $MS$ ) in

formula I (second paragraph of the section on method), using 6.5, the average thermal conductivity for females:

$$\begin{aligned}
 F &= 17 \times A \left( \frac{HI}{MR - MS} - 6.5 \right) \\
 &= 17 \times 1.72 \left( \frac{29.6}{36.86 - 34.27} - 6.5 \right) \\
 &= 29.2 \left( \frac{29.6}{2.59} - 6.5 \right) \\
 &= 29.2 (11.4 - 6.5) \\
 &= 29.2 \times 4.9 \\
 &= 143 \text{ cc./min.}
 \end{aligned}$$

Reduce the blood flow, 143 cc./min., to cubic centimeters per square meter per minute since the surface area ( $A$ ), 1.72 sq. M., is known:

$$\begin{aligned}
 F &= \frac{143}{1.72} \\
 &= 83 \text{ cc./sq.M./min.}
 \end{aligned}$$

The average peripheral blood flow per minute during this twenty minute period is thus obtained.

In order to use this method, certain data were required, namely, recordings of skin temperature, of rectal temperature, of oxygen consumption, of height and of body weight. The skin temperature was measured with the improved Hardy-Soderstrom radiometer,<sup>12</sup> the rectal temperature with a single junction copper-constantan thermocouple<sup>12</sup> and the oxygen consumption with a Benedict-Roth metabolism apparatus.<sup>13</sup> The basal metabolic rate was calculated from Mayo Foundation Standards for age and sex<sup>14</sup> and the surface area from the tables of Du Bois and Du Bois.<sup>15</sup>

The order in which data were recorded followed the plan already described.<sup>5</sup> All observations were made with the patients in a basal metabolic state. Six sets of skin and rectal temperatures were recorded at twenty minute intervals, from which the average peripheral blood flow for five twenty minute periods was calculated. The blood pressure and pulse rate were recorded during free intervals between temperature readings. The arm to tongue circulation time (decholin [sodium dehydrocholate]<sup>16</sup>) was measured after the last estimate of oxygen consumption had been made. Observations were made in exactly the same sequence for each patient at the environmental temperature<sup>5</sup> prevailing during the initial measurements. Observations were made before treatment was instituted and again at intervals after the administration of thyroid.

12. Hardy, J. D., and Soderstrom, G. F.: An Improved Apparatus for Measuring Surface and Body Temperature, *Rev. Scient. Instruments* **8**:418, 1937.

13. Roth, P.: Modifications of Apparatus and Improved Technique Adaptable to the Benedict Type of Respiration Apparatus, *Boston M. & S. J.* **186**:457, 1922.

14. Boothby, W. M.; Berkson, J., and Dunn, H. L.: Studies of the Energy of Metabolism of Normal Individuals: A Standard for Basal Metabolism with a Nomogram for Clinical Application, *Am. J. Physiol.* **116**:468, 1936.

15. Du Bois, D., and Du Bois, E. F.: A Formula to Estimate Approximate Surface Area if Height and Weight Be Known, *Arch. Int. Med.* **17**:863 (June) 1916.

16. Tarr, L.; Oppenheimer, B. S., and Sager, R. V.: The Circulation Time in Various Clinical Conditions Determined by the Use of Sodium Dehydrocholate, *Am. Heart J.* **8**:766, 1933.



in the basal metabolic rate and the peripheral blood flow, that is, increases with the giving of thyroid. The average pulse pressures showed similar changes in all but 1 patient (table 1).

*Circulation Time.*—The circulation time was prolonged before treatment. It became shorter during treatment with thyroid (table 1, fig. 2).

#### COMMENT

In a recent paper Stewart and Evans<sup>5</sup> showed that when the basal metabolic rate was elevated in patients with thyrotoxicosis the peripheral blood flow was also increased and during a fall in basal metabolic rate to normal with treatment there was a parallel decrease in peripheral blood flow. The observations now being reported furnish objective evidence that in the patients with myxedema these changes were of a reverse order. At a time when the basal metabolic rate was low in the untreated subjects, the peripheral blood flow was also decreased. During the progressive rise in basal metabolic rate with administration of thyroid there were successive and parallel increases in peripheral blood flow (fig. 2). Moreover, there was a linear relation between basal metabolic rate and peripheral blood flow, since with a progressive increase in basal metabolic rate there was an increase in peripheral blood flow (fig. 3). The wide scattering of peripheral blood flow at various levels for individual patients, particularly before treatment, appears to be due, in part, to different basal metabolic rates and, in part, to a different room temperature for each patient (fig. 2). Hick, Keeton, Glickman and Wall<sup>17</sup> and Hardy and Soderstrom<sup>10</sup> have shown a correlation between rise in environmental temperature and increase in the peripheral blood flow. Observations published recently by Stewart and Evans<sup>5</sup> are in agreement with their findings. For this reason care was exercised to keep the environmental temperature approximately the same during all observations on a single patient.

The skin of subjects suffering from myxedema appeared pale, cold and dry during the initial studies. Before treatment the average skin temperature and the peripheral blood flow were decreased, when the basal metabolic rate was low. The first studies after the administration of thyroid showed rises in skin temperature, peripheral blood flow and basal metabolic rate. Measurements made when the basal metabolic rate and peripheral blood flow had returned to normal in each patient showed further rises in skin temperature in 3 patients, essentially no change in 1 and a definite fall below the previous level in 2 (table 1).

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17. Hick, F. K.; Keeton, R. W.; Glickman, N., and Wall, H. C.: Cardiac Output, Peripheral Blood Flow and Blood Volume Changes in Normal Individuals Subjected to Varying Environmental Temperatures, Heating, Piping & Air Conditioning **11**:50, 1939.



It is evident, therefore, that increase in blood flow may occur at a time when there is a relative decrease in average skin temperature. These results are in agreement with the opinion expressed by Barr and Du Bois,<sup>18</sup> that it is possible for the body to lose more heat through a cool skin than through a warm one. Their subjects, studied in the Russell-Sage calorimeter, lost more heat by increased convection and evaporation, while the mechanism of heat loss in the patients in this investigation was not clear, since a calorimeter was not used. None experienced chilliness or exhibited sensible perspiration. It is well known

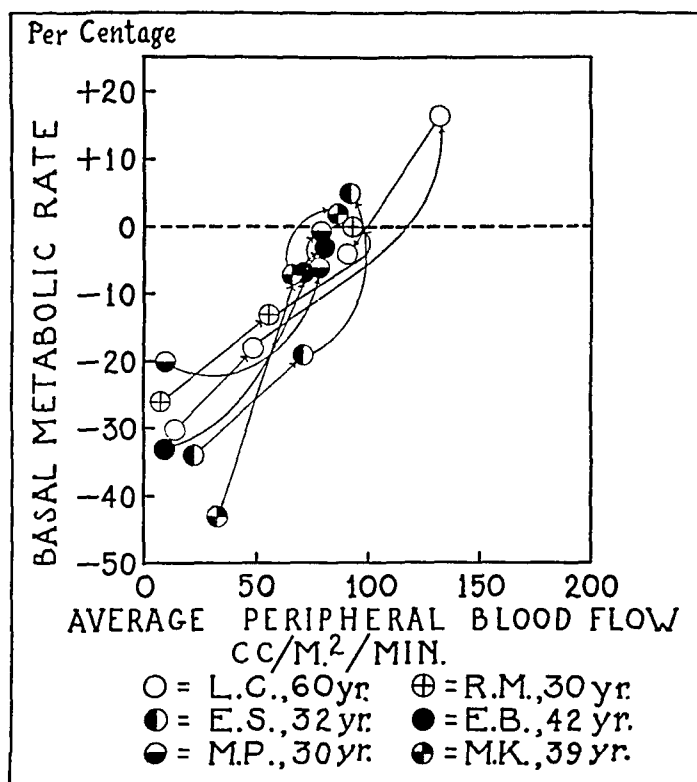


Fig. 3.—The data for peripheral blood flow are plotted against the corresponding basal metabolic rates. A linear relation is established, since with an increase in the basal metabolic rate the peripheral blood flow also increases.

that insensible perspiration may in itself bring about increased heat loss in the presence of a cool skin.

There appeared to be no direct relation between the temperature of the hands and the feet and the average skin temperature. The average temperature of the hands followed the average temperature of the body more closely, while the average temperature of the feet more

18. Barr, D. P., and Du Bois, E. F.: The Metabolism in Malarial Fever, Arch. Int. Med. **21**:627 (May) 1918.

nearly paralleled the changes in peripheral blood flow and in basal metabolic rate. The data for patient L. C. (fig. 1, table 1) are presented in detail to bring out these points.

The change in rectal temperature for each patient and for the group was much less marked than the alteration in average skin temperature. The average skin temperature for the group increased 0.82 C., while the rectal temperature showed a rise of only 0.02 C. from the time these patients were first seen until normal levels of basal metabolism were attained under treatment with thyroid (table 1).

Stewart, Deitrick and Crane<sup>1</sup> found that the cardiac output was low in patients with myxedema and increased to normal with a rise in basal metabolic rate on the administration of thyroid. The average cardiac outputs for the group on which they reported, determined at basal metabolic rates comparable to those at which our studies of peripheral blood flow were made, are shown in figure 4. The allotment of the cardiac output to the various organs in man is not known. In patients with myxedema, when the cardiac output is low, the amount allotted to the skin is also small. At the average basal metabolic rate of — 30 per cent about 1.3 per cent of the cardiac output was allotted to the skin. On return of cardiac output to a normal level during thyroid therapy the peripheral blood flow increased also, so that approximately 4 per cent of the output was allotted to the skin.

From Stewart, Deitrick and Crane's observations,<sup>1</sup> it appeared that the cardiac output per minute and per beat was decreased to such an extent in persons in a myxedematous state that in order for an adequate circulation to be maintained even for the lowered metabolic requirements of the organism, increase in the arteriovenous oxygen difference took place. In the investigation reported here, it has been demonstrated that the amount of blood allotted to the periphery was small when patients were suffering from myxedema. Increased flow of blood to the surface indicates increased heat loss. These data suggest that the mechanism responsible for the circulatory phenomena observed in patients with thyroid insufficiency is directed to the conservation of heat, for not only was the total cardiac output and that portion allocated to the body surface decreased but the velocity of blood flow was so low that the arteriovenous oxygen difference was increased. Boothby and Rynearson<sup>19</sup> have observed that in persons with thyrotoxicosis there was a greater increase in cardiac output than occurred in normal subjects as a result of a corresponding increase in oxygen consumption due to work. It has been shown that during this time the arteriovenous oxygen difference was

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19. Boothby, W. M., and Rynearson, E. H.: Increase in Circulation Rate Produced by Exophthalmic Goiter Compared with That Produced in Normal Subjects by Work, *Arch. Int. Med.* **55**:547 (April) 1935.

decreased. Recent observations of Stewart and Evans <sup>5</sup> showed a marked increase in peripheral blood flow during the hyperthyroid state. Since the total cardiac output and the peripheral blood flow were greater than the flow required for tissue metabolism (decreased arteriovenous oxygen difference), the mechanism in thyrotoxicosis was directed to increased heat loss, that is, opposite to that prevailing in myxedema.

The circulation time was estimated in order to have an additional objective measurement to correlate with values for peripheral blood flow.

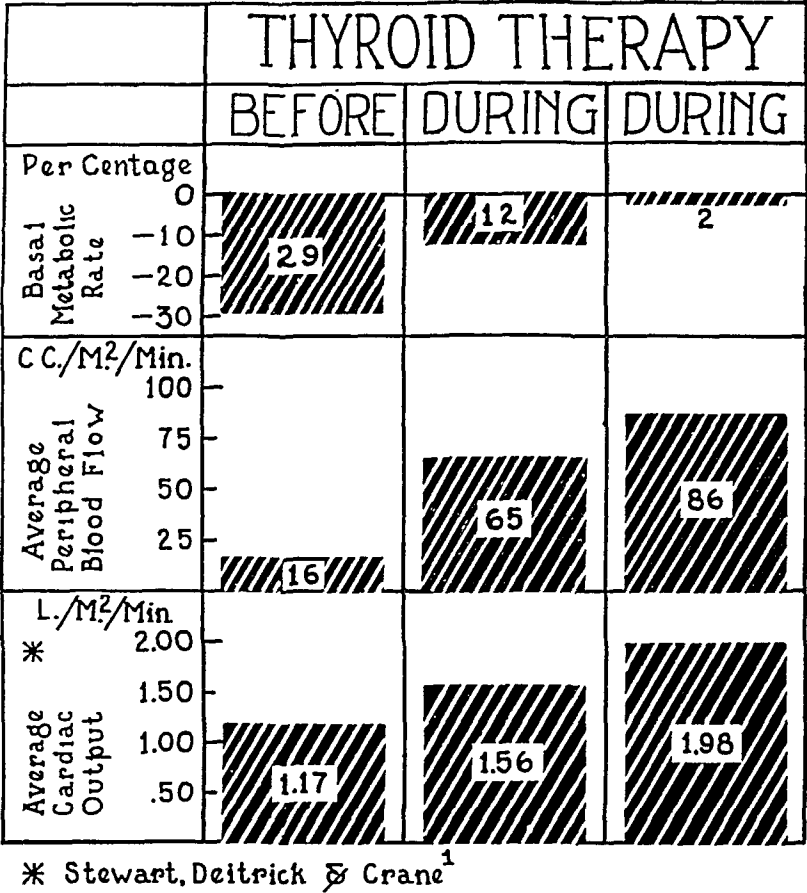


Fig. 4.—The average basal metabolic rate and the average peripheral blood flow for the whole group together with the average cardiac output of myxedematous patients at comparable levels of basal metabolism as reported by Stewart, Deitrick and Crane.<sup>1</sup>

These results demonstrate that in persons in a myxedematous state when the basal metabolic rate and the peripheral blood flow were decreased, the circulation time was prolonged. With a progressive increase in the basal metabolic rate during the administration of thyroid, there was a progressive decrease in circulation time (table 1, fig. 2).

## SUMMARY

Using a method which Stewart and Jack<sup>6</sup> and Stewart and Evans<sup>5</sup> have employed in earlier studies, we have made measurements of peripheral blood flow in 6 patients suffering from myxedema when they were first seen before treatment and again on several occasions during the course of thyroid therapy. In addition, certain other measurements of the circulation were recorded. The results are summarized as follows:

In persons in a myxedematous state when the basal metabolic rate was low, the peripheral blood flow in cubic centimeters per square meter per minute was decreased. With an increase in basal metabolic rate toward a normal level during the administration of thyroid, a progressive increase in peripheral blood flow occurred, so that a linear relation was maintained. These changes were opposite in direction to those observed in persons with thyrotoxicosis<sup>5</sup> and confirm the relation between peripheral blood flow and basal metabolic rate in these two diseases.

The cardiac output is decreased in patients with myxedema.<sup>1</sup> How the organs share this decrease is not known, but it is now shown that the amount of blood allotted to the periphery is decreased.

The circulation time before treatment was prolonged. During treatment progressive decreases took place. Shortening of circulation time roughly ran parallel to increase in basal metabolic rate and in peripheral blood flow.

The changes in pulse rate and pulse pressure followed roughly the increases in basal metabolic rate and peripheral blood flow.

For the most part, change in the average skin temperature followed the changes in basal metabolic rate and in peripheral blood flow.

No direct relation was observed between average skin temperature and the temperature of the hands and the feet.

No constant or significant changes in rectal temperature were observed during the several periods of study of each subject.

Conservation of heat has been suggested as an explanation for the decrease in peripheral blood flow in untreated patients suffering from myxedema.

# EFFECTIVE RENAL BLOOD FLOW, GLOMERULAR FILTRATION RATE AND TUBULAR EXCRETORY MASS IN ARTERIAL HYPERTENSION

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Interest in the relation of renal function and arterial hypertension, recognized since the time of Bright, has been greatly stimulated by the experimental work of Goldblatt and his associates,<sup>1</sup> who were able to produce permanent hypertension in animals by partial constriction of the main renal arteries. The experiments of Goldblatt and his co-workers have been successfully repeated in different ways by many authors, as cited by Goldblatt,<sup>2</sup> and the importance of normal renal circulation for the maintenance of normal blood pressure in animals appears to be an established fact.

Page and his associates<sup>3</sup> and Muñoz and Braun-Menendez and their associates,<sup>4</sup> reviving the original work of Tigerstedt and Berg-

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\* Mendelson Research Fellow.

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1. Goldblatt, H.; Lynch, J.; Hanzal, R. F., and Summerville, W. W.: Studies on Experimental Hypertension: I. The Production of Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischemia, *J. Exper. Med.* **59**:347, 1934. Goldblatt, H.: Studies on Experimental Hypertension: XII. The Experimental Production and Pathogenesis of Hypertension Due to Renal Ischemia, *Am. J. Clin. Path.* **10**:40, 1940.

2. Goldblatt, H.: Experimental Hypertension Induced by Renal Ischemia, in *Harvey Lectures, 1937-1938*, Baltimore, Williams & Wilkins Company, 1938, p. 237.

3. Page, I. H., and Helmer, O. M.: A Crystalline Pressor Substance (Angiotonin) Resulting from the Reaction Between Renin and Renin Activator, *J. Exper. Med.* **71**:29, 1940. Page, I. H.: Newer Aspects of Experimental Hypertension, in *Blood, Heart and Circulation*, Symposium Publication 13, American Association for the Advancement of Science, Washington, D. C., 1940, p. 239.

4. Muñoz, J. M.; Braun-Menendez, E.; Fasciolo, J. C., and Leloir, L. F.: The Mechanism of Renal Hypertension, *Am. J. M. Sc.* **200**:608, 1940. Braun-Menendez, E.; Fasciolo, J. C.; Leloir, L. F., and Muñoz, J. M.: The Substance Causing Renal Hypertension, *J. Physiol.* **98**:283, 1940.

man,<sup>5</sup> have offered further evidence of the importance of the renal circulation in hypertension by demonstrating the production in the kidney of a pressor substance, which they have called angiotonin, or hypertensin. The amount of angiotonin produced is increased when renal circulation is impaired. No convincing proof has been given, heretofore, that human hypertension is associated with reduced blood flow through the kidneys, although strong evidence indicates that this is the case. Blackman<sup>6</sup> performed autopsies on 50 patients who had had essential hypertension and found partial obstruction of the main renal artery due to arteriosclerotic plaques in 43 cases (86 per cent), whereas only 5 of 50 controls (10 per cent) showed similar lesions. Goldring and Smith and their associates<sup>7</sup> and, more recently, Chesley and Chesley<sup>8</sup> and McCann and Romansky<sup>9</sup> reported a marked reduction of the effective renal blood flow in patients with essential hypertension, as measured by the diodrast clearance method. Patients with hypertension due to coarctation of the aorta also have reduced effective renal blood flow (Friedman, Selzer and Rosenblum<sup>10</sup>).

The diodrast clearance method for the determination of effective renal blood flow was recently developed by Smith and his associates.<sup>11</sup> It is based on the principle that diodrast plasma clearance ( $C_D$ ) is practically complete at low concentration, and therefore is a measure of the flow of plasma through the active excretory renal tissue, excluding the inert renal tissue. The rate of glomerular filtration ( $C_{In}$ ) is measured by the clearance of inulin, a polysaccharide which is filtered through the glomeruli only and is not excreted or reabsorbed by the tubules. The filtration fraction (FF) is given by the  $C_{In}/C_D$  ratio and

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5. Tigerstedt, R., and Bergman, P. G.: Niere und Kreislauf, Skandinav. Arch. f. Physiol. **8**:223, 1898.

6. Blackman, S. S., Jr.: Arteriosclerosis and Partial Obstruction of the Main Renal Arteries in Association with Essential Hypertension in Man, Bull. Johns. Hopkins Hosp. **65**:353, 1939.

7. Goldring, W.; Chasis, H.; Ranges, H. A., and Smith, H. W.: Effective Renal Blood Flow and Functional Excretory Mass in Essential Hypertension, J. Clin. Investigation **17**:505, 1938. Smith, H. W.; Goldring, W.; Chasis, H., and Ranges, H. A.: Observations on the Effective Renal Blood Flow and Functional Excretory Mass in Man with Special Reference to Essential Hypertension, Am. J. Physiol. **123**:189, 1938.

8. Chesley, L. C., and Chesley, E. R.: Renal Blood Flow in Women with Hypertension and Renal Impairment, J. Clin. Investigation **19**:475, 1940.

9. McCann, W. S., and Romansky, M. J.: The Effect of Ptosis of the Kidneys on Blood Pressure, Renal Blood Flow and Glomerular Filtration, Tr. A. Am. Physicians **55**:240, 1940.

10. Friedman, M.; Selzer, A., and Rosenblum, H.: The Renal Blood Flow in Coarctation of the Aorta, J. Clin. Investigation **20**:107, 1941.

11. Smith, H. W.; Goldring, W., and Chasis, H.: The Measurement of the Tubular Excretory Mass, Effective Blood Flow and Filtration Rate in the Normal Human Kidney, J. Clin. Investigation **17**:263, 1938.

represents the fraction of the plasma cleared by the glomeruli. The maximal possible excretion of diodrast at a high concentration of this substance in the plasma is used as a measure of the active tubular excretory mass (diodrast  $T_m$ , or  $T_{mD}$ ).

The evidence supporting the accuracy of the methods has been reviewed extensively by Smith,<sup>12</sup> by Alving and Miller<sup>13</sup> and by Miller, Alving and Rubin<sup>14</sup> and needs no repetition.

The determination of effective renal blood flow per se does not give a complete picture of the circulatory conditions in the kidney. As a matter of fact, a reduced blood flow may be due to any of the following causes: 1. A reduced amount of normally perfused renal tissue (small normal kidneys, unilateral nephrectomy, etc.). Obviously in this case the circulation in the renal tissue is normal. The blood flow thus reduced is not associated with hypertension. 2. Uniform reduction in blood supply to all renal tissue. In this case hypertension should appear if the blood flow is sufficiently reduced. 3. Irregular distribution of blood to the renal tissue, with marked ischemia in one part of the kidney and comparatively normal circulation in other parts. Hypertension will appear under such circumstances if the amount of ischemic tissue is sufficiently great. As a matter of fact, strong evidence supports the hypothesis that neutralization, destruction or elimination of the chemical mediator of hypertension depends on the ratio of ischemic to normal tissue rather than on the amount of ischemic tissue alone.<sup>15</sup>

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12. Smith, H. W.: *The Physiology of the Kidney*, New York, Oxford University Press, 1937.

13. Alving, A. S., and Miller, B. F.: A Practical Method for the Measurement of Glomerular Filtration Rate (Inulin Clearance), *Arch. Int. Med.* **66**:306 (Aug.) 1940.

14. Miller, B. F.; Alving, A. S., and Rubin, J.: The Renal Excretion of Inulin at Low Plasma Concentrations of This Compound, and Its Relationship to the Glomerular Filtration Rate in Normal, Nephritic and Hypertensive Individuals, *J. Clin. Investigation* **19**:89, 1940.

15. Fasciolo, J. C.; Houssay, B. A., and Taquini, A. C.: The Blood Pressure Raising Secretion of the Ischaemic Kidney, *J. Physiol.* **94**:281, 1938. Katz, L. N.; Mendlowitz, M., and Friedman, M.: A Study of the Factors Concerned in Renal Hypertension, *Proc. Soc. Exper. Biol. & Med.* **37**:722, 1938. Rodbard, S., and Katz, L. N.: The Elimination of the Effect of the Chemical Mediator of Renal Hypertension, *Am. J. M. Sc.* **198**:602, 1939. Rodbard, S.; Katz, L. N., and Sokolov, M.: Reduction of Arterial Hypertension by Subcutaneous Implantation of Kidney Tissue, *Proc. Soc. Exper. Biol. & Med.* **44**:360, 1940. Williams, J. R., Jr.; Grollmann, A., and Harrison, T. R.: The Reduction of the Blood Pressure of Hypertensive Dogs by the Administration of Renal Extract, *Am. J. Physiol.* **130**:496, 1940. Grollmann, A.; Williams, J. R., Jr., and Harrison, T. R.: The Preparation of the Renal Extracts Capable of Reducing the Blood Pressure of Animals with Experimental Renal Hypertension, *J. Biol. Chem.* **134**:115, 1940. Blalock, A.: Experimental Hypertension, *Physiol. Rev.* **20**:159, 1940.

The conditions resulting from these three causes can be differentiated by the determination of the ratio of diodrast plasma clearance to tubular excretory mass ( $C_D/Tm_D$ ). When the excretory mass is reduced proportionally to the blood flow, as shown by a normal  $C_D/Tm_D$  ratio, the condition belongs in the first category and no hypertension is found. When the excretory mass is not reduced as much as the blood flow, as shown by a decreased  $C_D/Tm_D$  ratio, the condition falls in the second or third category and hypertension may develop. Finally, conditions could be classified in the third category if a procedure could be found which would increase the tubular excretory mass without proportionally increasing the blood flow. The tubular excretory mass may appear reduced when an insufficient amount of diodrast reaches the tubules of an ischemic part or parts of the kidney. Any procedure which would improve the distribution of blood to these parts would result, obviously, in an increased tubular excretory mass. This could occur without an actual increase in total effective renal blood flow on the basis of better distribution of the blood, resulting in a decreased  $C_D/Tm_D$  ratio. That this is a possibility in essential hypertension is indicated by the rapidly changing distribution of blood in other vasospastic disorders, such as Raynaud's disease.

With the working hypothesis that a spasm of the renal vessels is the cause of hypertension in man, and in the hope of curing this disease by increasing the blood flow through the kidneys or improving its distribution to the renal tissue, Peet and associates,<sup>16</sup> suggested the surgical denervation of the kidneys by means of splanchnicectomy and lower dorsal sympathetic ganglionectomy. We are studying the renal circulation of patients thus treated surgically for hypertension before operation and approximately two weeks and six months after the operation.

The purpose of this paper is to report the results of the preoperative study of 20 of these patients, ranging in age from 26 to 54 years.

#### METHOD

*Preliminary Studies and Choice of the Patients.*—Each patient was examined in the departments of medicine, ophthalmology, cardiology and roentgenology. Renal function studies, besides the routine urinalysis, included a short concentration test (eighteen hours), measurement of urea clearance and determination of the nonprotein nitrogen content of the blood. Only patients without signs of cardiac decompensation or acute renal disease were included in this study.

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16. Peet, M. M.: Splanchnic Section for Hypertension: A Preliminary Report, Univ. Hosp. Bull., Ann Arbor **1**:17, 1935. Peet, M. M.; Woods, W. W., and Braden, S.: The Surgical Treatment of Hypertension, J. A. M. A. **115**:1875 (Nov. 30) 1940.



The blood pressure was taken on admission to the hospital and several times after at least twenty-four hours of rest in bed, according to a standard procedure.<sup>17</sup> The cold pressor test and abdominal diathermy were used in an attempt to ascertain the degree of vasomotility and thus differentiate patients whose hypertension was due to vasospasm from those whose hypertension was due to arteriosclerosis. The cold pressor test was performed according to the technic of Hines.<sup>18</sup> Diathermy was applied by means of electrode pads in the region of the kidneys for thirty to forty-five minutes, and the lowest blood pressure reached was recorded.

Further information on the condition of the blood vessels was obtained by measuring the thickness of the wall and the diameter of the lumen of the arterioles in biopsy specimens of intercostal tissue. Material for biopsy was obtained during the operation for splanchnicectomy and studied according to the method described by Morlock.<sup>19</sup> The results are given as a ratio of the thickness of the wall to the diameter of the lumen. Only arterioles cut in exact cross section and varying between 20 and 150 microns of total diameter were used. At least five arterioles per patient were measured and the ratios averaged. Objections to the reliability of this method have been raised.<sup>20</sup> We feel, however, that the results are comparable because the biopsy material was collected and fixed under uniform conditions with all patients under general anesthesia.

*Preparation of the Patient.*—Two liters of fluid was given to the patient the afternoon and evening prior to the experiment. All medication was discontinued for twenty-four hours. Two liters of fluid was given in the morning of the test, the patient having his last drink approximately ninety minutes before the first collection of urine. Neither coffee or tea nor breakfast was allowed.

*Clearance Test for Determining Effective Renal Blood Flow and Filtration Rate.*—Thirty-five cubic centimeters of a 10 per cent solution of inulin and 5 to 8 cc. of a 35 per cent solution of diodrast were dissolved in 1,000 cc. of physiologic solution of sodium chloride for continuous intravenous injection. The amount of diodrast was reduced proportionally to the urea clearance when this was below 75 per cent and to the surface area. A sample of urine was collected; then 30 cc. of blood was taken from a cubital vein and the infusion started through the same needle. Samples of blood and urine were used for blanks in the determination of inulin and diodrast. Fifteen cubic centimeters of a 10 per cent solution of inulin and 1.5 cc. of diodrast were injected directly into the vein through the rubber tubing as a priming dose. The rate of infusion was then adjusted to 5 cc. per minute by means of a special tubular clamp about 2 inches (5 cm.) long. Twenty minutes was allowed for blood levels of inulin and diodrast to become constant. During this interval, the patient was catheterized, the urine discarded and the bladder washed with a known amount of a physiologic solution of sodium chloride and then emptied with air. The first specimen of urine was collected in about ten minutes. Five minutes before collecting it 30 cc. of blood

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17. Standardization of Blood Pressure Readings: Joint Recommendations of the American Heart Association and the Cardiac Society of Great Britain and Ireland, *Am. Heart J.* **18**:95, 1938.

18. Hines, E. A., Jr.: Technique of the Cold Pressor Test, *Proc. Staff Meet., Mayo Clin.* **14**:185, 1939; The Significance of Vascular Hyperreaction as Measured by the Cold Pressor Test, *Am. Heart J.* **19**:408, 1940.

19. Morlock, C. G.: Arterioles of the Pancreas, Liver, Gastrointestinal Tract and Spleen in Hypertension, *Arch. Int. Med.* **63**:100 (Jan.) 1939.

20. Moritz, A. R., and Oldt, M. R.: Arteriolar Sclerosis in Hypertensive and Non-Hypertensive Individuals, *Am. J. Path.* **13**:679, 1937.

was taken from the cubital vein of the other arm and transferred to an oxalated tube. According to this technic, urine was collected every ten minutes for eight samples and blood every twenty minutes for four samples. The time of collection was accurately recorded. The urine was immediately measured and diluted to a 1:10 concentration to avoid precipitation of inulin. The flow of urine per minute was computed, after subtracting the volume of saline solution used as a wash. The blood was centrifuged immediately to avoid diffusion of inulin and diodrast into the blood cells. A hematocrit reading was made.

The blood pressure was taken every five to ten minutes; the temperature and pulse, every thirty minutes. The rate of infusion was checked at intervals and was kept constant.

*Measurement of Tubular Excretory Mass.*—After six to eight clearance periods 20 cc. of diodrast was injected into the vein through the rubber tubing. Ten cubic centimeters of diodrast was added to every 100 cc. of infusion solution left in the intravenous injection bottle. The rate of infusion was readjusted to 5 cc. per minute. Twenty minutes was allowed for blood levels to become constant again, and the bladder was emptied and washed as previously described. Specimens of blood and urine were taken according to the aforementioned technic for three clearance periods.

*Chemical Determinations.*—Diodrast: Five cubic centimeters of plasma or urine was placed in a nickel crucible, dried overnight at 90 C. and digested with about 10 Gm. of sodium hydroxide pellets. The iodine was determined by the method of Kendall.<sup>21</sup> The concentration of diodrast iodine was less than 2 mg. per hundred cubic centimeters of plasma. For the determination of tubular excretory mass, the diodrast iodine in the plasma was raised above 15 mg. per hundred cubic centimeters.

Inulin: The method of Alving,<sup>22</sup> which was recently modified by Miller, Alving and Rubin,<sup>14</sup> was used for the determination of inulin. The concentration of inulin was approximately 8 to 15 mg. per hundred cubic centimeters of plasma.

Blood flow, filtration rate and tubular excretory mass were calculated according to the method and formulas given by Smith, Goldring and Chasis.<sup>11</sup> All data were corrected proportionally to the average body surface of 1.73 square meters and to a body temperature of 98.5 F.

## RESULTS

Effective renal blood flow and filtration rate were determined for 20 patients with hypertension. For 10 subjects tubular excretory mass was also determined. The filtration fraction and the ratios of plasma flow to tubular mass ( $C_D/Tm_D$ ) and filtration rate to tubular mass ( $C_{In}/Tm_D$ ) were computed from these data (table 1). Seven normal subjects without hypertension were used as controls. A larger number of controls was felt unnecessary, owing to the fact that the results were comparable to those found in the literature (tables 2 and 3).

The effective renal blood flow averaged 549 cc. per minute (165 to 1,088.5 cc.) in hypertensive patients, which is a reduction to almost

21. Kendall, E. C.: Determination of Iodine in Connection with Studies in Thyroid Activity, *J. Biol. Chem.* **43**:149, 1920.

22. Alving, A. S.; Rubin, J., and Miller, B. F.: A Direct Colorimetric Method for the Determination of Inulin in Blood and Urine, *J. Biol. Chem.* **127**:609, 1939.

TABLE 1.—Data on Hypertensive Patients

Patient	Sex	Age, Yr.	Eyegrounds K-W * Changes †	Arterioles, Wall/ Lumen	Effective Renal Flow, Cc. per Min.	Filtration Rate, Cc. per Min.	FF, ‡ per Cent	Ratio of Ratio of			Blood Pressure, Mm. Hg		Drop in Blood Pressure During Diath- ermy, Mm. Hg	Rise in Blood Pressure During Cold Pressor Test, Mm. Hg	Con- centra- tion of Urine	Urea Clear- ance, Nitrogen, per Cent 100 Cc.	Non- protein Nitrogen, Mg. per 100 Cc.	
								Tubular Excre- tory Mg., Iodine per Min.	Excre- tory Mass	Clear- ance to Excre- tory Mass	On Admis- sion	After Rest in Bed						
1	F	30	IV	2.007	165.00	47.05	46.78	10.70	10.50	4.27	290/190	270/180	276/179	26/30	20/10	1.013	38.0	34.2
2	F	34	IV	1.050	201.80	.....	.....	.....	.....	.....	220/140	204/130	210/136	2/16	20/6	1.021	111.0	31.7
3	M	53	IV	1.139	250.00	46.50	53.00	7.92	23.50	5.87	254/135	230/135	227/138	2/0	30/25	1.017	62.0	40.0
4	F	42	IV	1.755	250.90	45.80	27.83	.....	.....	.....	259/120	172/110	219/127	28/16	22/14	1.016	66.0	35.5
5	M	39	IV	1.065	261.90	.....	.....	20.15	8.45	.....	210/150	210/110	200/144	22/17	45/16	1.029	63.5	25.5
6	M	34	III	1.600	433.60	87.90	37.70	.....	.....	.....	200/130	203/131	171/119	2/0	30/6	1.021	118.0	39.5
7	F	54	IV	1.703	434.50	113.80	37.58	.....	.....	.....	280/140	210/100	259/132	4/2	15/15	1.031	95.0	31.4
8	F	45	III	1.117	463.20	175.80	63.88	40.42	6.84	4.16	240/150	182/90	189/114	35/10	13/30	.....	96.5	31.4
9	F	46	III	0.601	496.70	85.00	27.03	30.60	10.98	2.78	220/130	204/118	212/126	33/22	15/15	1.038	86.0	32.5
10	M	51	IV	0.905	506.70	.....	.....	.....	.....	.....	190/120	118/85	118/87	16/5	10/16	1.023	47.0	30.9
11	M	37	III	0.761	528.80	83.10	26.68	.....	.....	.....	245/145	200/100	184/133	2/15	30/45	1.026	101.0	32.9
12	F	40	III	0.750	613.10	61.40	15.44	.....	.....	.....	185/140	122/62	127/105	28/10	42/35	1.020	96.0	28.0
13	M	36	III	0.819	649.80	73.20	19.40	.....	.....	.....	210/170	190/125	184/127	8/6	10/15	1.026	88.0	33.1
14	F	39	III	0.901	669.50	119.80	29.43	42.84	9.75	2.80	225/130	180/104	203/123	.....	47/27	1.016	101.0	26.4
15	F	52	III	1.367	681.80	120.60	30.48	28.20	13.90	4.28	230/130	160/96	188/102	.....	20/5	1.023	80.0	13.4
16	F	44	III	0.571	788.70	109.50	24.74	34.69	13.11	3.18	200/120	160/100	158/92	.....	20/5	1.023	80.0	13.4
17	M	28	Normal	1.051	801.00	125.80	25.90	25.16	18.60	1.95	210/130	132/106	148/106	16/1	32/15	1.040	125.0	29.7
18	F	42	II	1.151	807.60	143.90	20.90	.....	.....	.....	215/135	190/110	198/126	34/12	100/50	1.030	133.0	28.7
19	F	39	III	0.991	816.00	74.50	15.50	.....	.....	.....	210/120	160/90	171/108	52/22	30/20	1.039	104.0	37.5
20	F	26	Normal	0.567	1,088.50	140.90	22.30	33.17	19.4	4.25	190/110	120/60	162/81	11/6	10/10	1.042	108.0	26.7

\* K-W, the Keith-Wagener classification of hypertensive patients, based on the condition of the ocular fundus.

† H, hemorrhages; Ex, exudates; Ed, papilledema; Sp, angiospasm, and Sc, sclerosis.

‡ FF, filtration fraction; it is given by the ratio between the clearance of inulin and the clearance of diodrast and represents the fraction of the plasma cleared by the glomeruli.

TABLE 2.—Data on Nonhypertensive Subjects

Patient	Sex	Age, Yr.	Blood Pressure, Mm. Hg	Effective Renal Blood Flow, Cc. per Min.	Filtration Rate, Cc. Plasma per Min.	FF,* per Cent	Tubular Excretory Mass, Mg. Iodine per Min.	Ratio of Diodrast Clearance to Excretory Mass	Ratio of Inulin Clearance to Excretory Mass
1	M	55	131/86	717.08	81.54	21.52	.....	.....	....
2	M	22	116/72	756.60	109.80	23.73	47.3	9.76	2.23
3	M	56 †	.....	889.00	97.00	20.96	28.2	18.60	3.44
4	M	49	120/82	1,268.30	127.30	16.74	.....	.....	....
5	M	32	136/68	1,095.20	108.31	16.57	31.8	22.4	3.38
6	M	26	124/82	1,534.50	108.40	12.51	48.60	19.45	2.30
7	M	..	137/70	1,159.60	185.90	24.23	45.80	16.95	4.04
Average			128/76	1,059.95	116.89	18.18	40.22	16.23	3.08

\* FF, filtration fraction; it is given by the ratio between the clearance of inulin and the clearance of diodrast and represents the fraction of the plasma cleared by the glomeruli.

† The data on this patient were obtained separately for each kidney by means of a ureteral catheter. The values given here are the total of the two determinations.

TABLE 3.—Data on Effective Renal Blood Flow, Glomerular Filtration Rate and Tubular Excretory Mass Obtained by Different Authors for Nonhypertensive Subjects

Author	No. and Sex of Subjects	Effective Renal Blood Flow, Cc. per Min.	Filtration Rate, Cc. Plasma per Min.	FF,* per Cent	Tubular Excretory Mass, Mg. Iodine per Min.	Ratio of Diodrast Clearance to Excretory Mass	Ratio of Inulin Clearance to Excretory Mass
Foa, Woods and Peet.....	7 M	1,060.0 (717.1- 1,534.5)	116.89 (81.54- 185.9)	18.18 (12.51- 24.23)	40.22 (28.2- 48.0)	16.23 (9.76- 22.4)	3.08 (2.23- 4.04)
Goldring, W.; Ohasis, H.; Ranges, H. A., and Smith, H. W.: J. Clin. Investigation 19: 739, 1940	43 M	1,189.0 (521- 1,780)	130.0 (76- 199)	18.9 (14.1 25.4)	53.3 (38.8- 72)	22.3 (16- 29.5)	2.57 (2.09- 3.12)
Chesley, L. O., and Chesley, E. R.: Am. J. Physiol. 127: 731, 1939	13 F	850.0 (694- 1,233)	.....	20.4 (15.2- 24.5)	.....	.....	.....
Miller, Alving and Rubin <sup>14</sup> .....	5 M 1 F	.....	111.5 (74- 150)	.....	.....	.....	.....
White, H. L.; Findley, T., Jr., and Edwards, J. C.: Proc. Soc. Exper. Biol. & Med. 43: 11, 1940	11	497 †	.....	.....	44 †	.....	.....
Friedman, Selzer and Rosenblum <sup>10</sup>	6 M  5 F	1,288 (910- 1,640)  986 (805- 1,230)	124.4 (110- 137)  125.8 (116.5- 153)	17.8 (12.9- 22.7)  19.0 (15- 22)	.....  .....	.....  .....	.....  .....
McCann and Romansky <sup>9</sup> .....	2 M 3 F	1,162.6 (1,027- 1,323)	134.6 (113- 159)	.....	.....	.....	.....

\* FF, filtration fraction; it is given by the ratio between the clearance of inulin and the clearance of diodrast and represents the fraction of the plasma cleared by the glomeruli.

† The average result for 58 clearance periods.

‡ The average result for 3 subjects.

one-half the value of 1,060 cc. per minute (717 to 1,534 cc.) found for normal subjects. The filtration rate for patients with hypertension averaged 97.5 cc. of plasma per minute (45.8 to 175.8 cc.), which is less than the normal rate of 116.9 cc. per minute (81.54 to 185.9 cc.), but the reduction is not proportional to the reduction in blood flow. The filtration fraction, therefore, was increased from the normal level of 18.18 per cent (12.51 to 24.23 per cent) to the hypertensive level of 31.2 per cent (15.44 to 63.88 per cent). The tubular excretory mass was reduced but not significantly in most cases; for hypertensive subjects the average was 27.4 mg. of iodine per minute (7.92 to 42.84 mg.), as compared with 40.22 mg. per minute (28.2 to 48 mg.) for normal subjects. The ratio of plasma flow to tubular excretory mass ( $C_D/Tm_D$ ) in patients with hypertension was low, indicating a low blood flow per unit of functioning renal tissue; the average value was 13.54 (6.84 to 23.5), as compared with the normal ratio of 16.23 (9.76 to 22.4). The high ratio of filtration rate to tubular excretory mass ( $C_{In}/Tm_D$ ) shows that in hypertension there is a high filtration rate per unit of functioning renal tissue; the average value was 4.09 (2.78 to 5.87), as compared with the normal ratio of 3.08 (2.23 to 4.04). These ratios were computed on the basis of plasma filtration rate and plasma flow.

Table 1 includes also the data on the results of abdominal diathermy and the cold pressor test, concentration of urine, urea clearance, non-protein nitrogen content of the blood, condition of the eyegrounds and ratio of the thickness of the wall to the diameter of the lumen of the arterioles in the biopsy specimens.

#### COMMENT

A comparison of our results for nonhypertensive subjects and those obtained by other authors is given in table 3. Our results fall within the range of those of other investigators. The figures reported by Chesley and Chesley for blood flow are lower, and the discrepancy can be explained only partially by the fact that their patients were all females. Our values for tubular excretory mass are within the range of values obtained by Smith and his associates, but our average is lower and closer to the values reported by White, Findley and Edwards; however, the  $C_D/Tm_D$  and  $C_{In}/Tm_D$  ratios are comparable to those given by Smith and co-workers. The small number of determinations is probably partially responsible for the difference, since the concentration of iodine in the blood was in all cases well above 15 mg. per hundred cubic centimeters, the minimum required for the saturation of the kidneys.

A comparison of the results obtained for subjects without hypertension and those obtained for patients with hypertension shows that

the latter had a greatly reduced effective renal blood flow, that the filtration rate was decreased but less proportionally than the blood flow and that therefore the filtration fraction was increased. The tubular excretory mass was not significantly reduced in most cases. The filtration rate per unit of excretory mass ( $C_{In}/Tm_D$ ) was elevated. The plasma flow per unit of excretory mass ( $C_D/Tm_D$ ) was reduced. Analogous results were obtained previously by Goldring, Smith and associates<sup>7</sup> and by Chesley and Chesley.<sup>8</sup>

High systemic blood pressure alone should result in an increased flow of blood through any organ. Pickering<sup>23</sup> and Prinzmetal and Wilson<sup>24</sup> have shown that patients with essential hypertension have a normal flow of blood through their extremities. Therefore, they concluded, the lumens of the blood vessels must be reduced proportionately to compensate with an increased peripheral resistance for the increased blood pressure. Since in our patients there was a reduction of renal blood flow, the vasoconstriction must have been even more severe in the kidneys than in the muscles or skin. As pointed out by Goldring, Smith and associates,<sup>7</sup> the increased rate of glomerular filtration relative to blood flow might be due to (1) the persistence of tubules which have lost their excretory capacity and serve merely as conduits for their still functioning glomeruli; (2) increased systemic blood pressure, or (3) hypertonus or sclerotic narrowing of the efferent glomerular arterioles.

The first explanation does not seem likely, especially when one considers that vasomotor disturbances are present in the kidney at an early stage of hypertension, when no signs of tubular damage are present. Increased systemic blood pressure alone, although certainly a contributing factor, is not sufficient to explain the phenomenon. Corcoran and Page<sup>25</sup> have shown experimentally that it is possible to induce a marked increase in blood pressure by the administration of pitressin and atropine, with only minor changes in filtration rate. Narrowing of the efferent glomerular arterioles is, therefore, an important, if not the most important, factor in the determination of the ischemia and the increased vascular resistance in the renal tissue. The predominant importance of the efferent arterioles for the regulation of the glomerular hemodynamics in nonhypertensive persons has been

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23. Pickering, G. W.: The Peripheral Resistance in Persistent Arterial Hypertension, *Clin. Sc.* **2**:209, 1936.

24. Prinzmetal, M., and Wilson, C.: The Nature of the Peripheral Resistance in Arterial Hypertension with Special Reference to the Vasomotor System, *J. Clin. Investigation* **15**:63, 1936.

25. Corcoran, A. C., and Page, I. H.: The Effects of Renin, Pitressin, and Pitressin and Atropin on Renal Blood Flow and Clearance, *Am. J. Physiol.* **126**: 354, 1939.

pointed out by Chasis, Smith and their associates<sup>26</sup> and is supported by some anatomic evidence.<sup>27</sup> Any decrease in blood flow is accompanied by a compensatory change in glomerular pressure, with the result that the filtration rate remains relatively constant, and a normal renal function can be maintained even in the presence of a relatively marked reduction in blood flow. Thus, the vessels of the kidney appear to maintain in hypertension the same degree of independence that they have under normal physiologic conditions.

The ratios of  $C_D/Tm_D$  and  $C_{In}/Tm_D$  show that hypertensive patients have a high filtration rate and a low blood flow per unit of functioning renal tissue (relative ischemia).

#### CONCLUSIONS

The results seem to indicate that hypertension is a systemic vascular disease, affecting equally the vessels of the eyegrounds, muscles and kidneys, associated with ischemia of the renal tissues and increased glomerular pressure. At an early stage of the disease, when signs of damage to the renal function are still absent, renal ischemia may already be detectable. However, we have no definite evidence as yet on which to decide whether renal ischemia is a causal factor in human hypertension or simply one aspect of the systemic vascular disease.

We believe that a correlation between the severity of the disease, the reduction in effective renal blood flow and the values for filtration fraction and tubular excretory mass is not justifiable as yet. However, an attempt at such a correlation can be made by dividing the patients into two groups (table 1).

The first group includes patients 1 to 11; these all had a blood flow lower than 549 cc. per minute, our average value for renal blood flow in hypertensive patients. The filtration fraction averaged 40.06 per cent for this group; the tubular excretory mass averaged 21.96 mg. of iodine per minute. The blood pressure on admission to the hospital averaged 239 systolic and 141 diastolic; after rest in bed the average

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26. Chasis, H.; Ranges, H. A.; Goldring, W., and Smith, H. W.: The Control of Renal Blood Flow and Glomerular Filtration in Normal Man, *J. Clin. Investigation* **17**:683, 1938. Smith, H. W.; Rovenstine, E. A.; Goldring, W.; Chasis, H., and Ranges, H. A.: The Effects of Spinal Anesthesia on the Circulation in Normal, Unoperated Man with Reference to the Autonomy of the Arterioles and Especially Those of Renal Circulation, *ibid.* **18**:319, 1939. Smith, H. W.: Kidney, in Luck, J. M., and Hall, V. E.: *Annual Review of Physiology*, Stanford University, Calif., Stanford University Press, 1939, vol. 1, p. 503. Smith, H. W.; Chasis, H.; Goldring, W., and Ranges, H. A.: Glomerular Dynamics in the Normal Human Kidney, *J. Clin. Investigation* **19**:751, 1940.

27. Bensley, R. D.: The Efferent Vessels of the Renal Glomeruli of Mammals as a Mechanism for the Control of Glomerular Activity and Pressure, *Am. J. Anat.* **44**:141, 1929.

blood pressure for this group dropped to 198 systolic and 120 diastolic. All of the patients except 3 in this group had a fixed level of hypertension or a blood pressure fluctuating at high levels, which was scarcely influenced by rest in bed. Five of them had a markedly reduced urea clearance. All except 3 had reduced power of concentrating urine. The nonprotein nitrogen content of the blood averaged 33.2 mg. per hundred cubic centimeters. Examination of the eyegrounds showed

TABLE 4.—*Comparison of Average Results for Patients with Less Than Five Hundred and Forty-Nine Cubic Centimeters of Effective Renal Blood Flow Per Minute (Group I) and for Patients with More Than Five Hundred and Forty-Nine Cubic Centimeters of Flow Per Minute (Group II)*

	Group I, Average	Group II, Average	Total, Average
Age, years.....	44	38	41
Effective renal blood flow, cc. per minute *.....	363.00	775.5	549.00
Filtration rate, cc. plasma per minute †.....	85.60	107.7	97.5
FF, ‡ per cent.....	40.06	23.23	31.2
Tubular excretory mass, mg. iodine per minute.....	21.96	32.85	27.4
Diodrast clearance/excretory mass.....	12.05	15.02	13.54
Inulin clearance/excretory mass.....	4.35	3.89	4.09
Blood pressure, mm. Hg			
On admission.....	239/141	212/134	227/138
After rest in bed.....	198/120	157/ 95	180/109
During test.....	206/129	171/108	190/120
Drop during diathermy.....	16/12	26/10	20/10
Rise during cold pressor test.....	21/18	35/21	27/20
Urine concentration.....	1.024	1.030	1.027
Urea clearance, per cent.....	80.4	104.6	91.4
Nonprotein nitrogen, Mg./100 cc.....	33.2	28.6	31.2
Arterioles, ratio wall/lumen.....	1.248	0.9075	1.094
Examination of the eyegrounds			
Keith-Wagener classification.....	7 Group IV 4 Group III	6 Group III 1 Group II 2 normal	
Changes.....	Retinitis, 9 Spasm, 2	Spasm and sclerosis, 5 Sclerosis, 1 Retinitis, 1 Normal, 2	

\* Diodrast clearance.

† Inulin clearance.

‡ FF, filtration fraction; it is given by the ratio between the clearance of inulin and the clearance of diodrast and represents the fraction of the plasma cleared by the glomeruli.

hemorrhagic retinitis with exudates in all but 2 cases. Seven patients had edema of the optic disks; of these, 5 had the lowest values for renal blood flow, less than one-fourth the average normal value. It will be noted that all the patients of this group had at least one of the aforementioned severe symptoms. The ratio of the wall to the lumen of the arterioles of the intercostal tissue ranged between 0.601 and 2.007 (average, 1.248).

The second group includes patients 12 to 20, who had a renal blood flow of more than 549 cc. per minute. The filtration fraction aver-



aged 23.23 per cent; the tubular excretory mass averaged 32.85 mg. of iodine per minute. The blood pressure on admission to the hospital averaged 212 systolic and 134 diastolic, and it dropped to 157 systolic and 95 diastolic after rest in bed. All of these patients had a fluctuating type of blood pressure, had a drop in pressure after rest in bed and responded to different stimuli, such as abdominal diathermy, exercise, mental arithmetic and the cold pressor test. All of them had normal urea clearance, and 5 of them had normal power of urine concentration. The nonprotein content of the blood nitrogen averaged 28.6 mg. per hundred cubic centimeters. The changes in the eyegrounds were definitely less severe in this group. Examination showed normal fundi in 2 patients and hemorrhagic retinitis with exudates in 1 patient only. Five patients had angiospasm and sclerosis of the retinal vessels. The ratio of the wall to the lumen of the arterioles in the biopsy material ranged between 0.567 and 1.367 (average, 0.9075).

The results in tables 1 and 4 show a good correlation between effective renal blood flow, filtration fraction, condition of the eyegrounds, thickening of the wall of the systemic arterioles and, after rest in bed, blood pressure. As good a correlation cannot be made from a comparison of these factors and urine concentration, urea clearance and the nonprotein nitrogen content of the blood except in the extreme cases. One would expect this to be the case, since blood pressure, condition of the eyegrounds, condition of the systemic arterioles and renal blood flow are all primary aspects of the vascular disease, whereas urine concentration, urea clearance and the nonprotein nitrogen in the blood are altered secondarily.

We feel, therefore, that the measurement of renal blood flow and filtration fraction may prove to be valuable in determining the severity of hypertension.

#### SUMMARY

Effective renal blood flow, filtration rate and renal tubular excretory mass have been determined for 20 patients with hypertension and for 7 nonhypertensive subjects.

The results indicate that arterial hypertension in man is accompanied by reduced renal blood flow, owing to increased resistance of the efferent glomerular vessels. However, they do not prove whether ischemia is a causal factor in hypertension or is simply one aspect of the systemic vascular disease. The relation between the function of the renal vessels and other clinical and morphologic observations is discussed. The latter include data on blood pressure, the condition of the eyegrounds, urine concentration, urea clearance, nonprotein nitrogen content of the blood and ratio of the wall to the lumen of the arterioles of intercostal tissue obtained for biopsy.

The patients are being studied approximately two weeks and six months after supradiaphragmatic splanchnicectomy and lower dorsal sympathetic ganglionectomy. The results of postoperative study will be reported in the future.

Dr. R. H. Lyons and Dr. E. Tuftland, of William J. Seymour Hospital, Eloise, Mich., procured nonhypertensive subjects for this study; the Winthrop Chemical Co., Inc., provided a supply of diodrast, and Liebel-Flarsheim Co. lent us a short wave diathermy machine.

# USE OF ALPHA TOCOPHEROL IN THE TREATMENT OF NEUROMUSCULAR DISORDERS

ALBERT J. LUBIN, M.D.

SAN FRANCISCO

On the basis of experimental paralyses produced in animals by Evans and Burr,<sup>1</sup> Einarson and Ringsted<sup>2</sup> and others, vitamin E and alpha tocopherol, an alcohol isolated from wheat germ oil having apparently all of the properties of the vitamin, have been rather widely advocated as therapeutic agents for a variety of diseases of the neuromuscular system, especially amyotrophic lateral sclerosis and progressive muscular dystrophy. The favorable clinical reports of Bicknell<sup>3</sup> and Wechsler<sup>4</sup> have been followed by those of Stone,<sup>5</sup> Vilter, Aring and Spies,<sup>6</sup> and Rosenberger<sup>7</sup> and by a considerable body of literature distributed by various pharmaceutical companies and, indeed, by the lay press. However,

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From the Department of Medicine (Division of Neuropsychiatry), Stanford University School of Medicine.

The synthetic alpha tocopherol was supplied by Merck & Co., Inc. and by Hoffmann-Laroche, Inc. through the cooperation of Dr. Herbert M. Evans, of the University of California.

1. Evans, H. M., and Burr, G. O.: Development of Paralysis in the Suckling Young of Mothers Deprived of Vitamin E, *J. Biol. Chem.* **65**:273-279 (Jan.) 1928.

2. Einarson, L., and Ringsted, A.: Effect of Chronic Vitamin E Deficiency on the Nervous System and the Skeletal Musculature in Adult Rats: A Neurotropic Factor in Wheat Germ Oil, London, Humphrey Milford, 1938.

3. Bicknell, F.: Vitamin E in the Treatment of Muscular Dystrophies and Nervous Diseases, *Lancet* **1**:10-13 (Jan. 6) 1940.

4. Wechsler, I. S.: Recovery in Amyotrophic Lateral Sclerosis Treated with Tocopherols (Vitamin E): Preliminary Report, *J. A. M. A.* **114**:948-950 (March 16) 1940; The Treatment of Amyotrophic Lateral Sclerosis with Vitamin E (Tocopherols), *Am. J. M. Sc.* **200**:765-778 (Dec.) 1940.

5. Stone, S.: Treatment of Muscular Dystrophies and Allied Conditions: Preliminary Report on Use of Vitamin E (Wheat Germ Oil), *J. A. M. A.* **114**:2187-2191 (June 1) 1940; Vitamin E in the Treatment of Muscle Disorders of Infancy and Childhood, *J. Pediat.* **18**:310-316 (March) 1941.

6. Vilter, R. W.; Aring, C. D., and Spies, T. D.: A Case of Arsenic Peripheral Neuritis Treated with Synthetic Vitamin B<sub>6</sub> and Alpha-Tocopherol, *J. A. M. A.* **115**:209 (July 20) 1940. Spies, T. D., and Vilter, R. W.: A Note on the Effect of Alpha-Tocopherol (Vitamin E) in Human Nutrition, *South. M. J.* **33**:663-664 (June) 1940.

7. Rosenberger, A. I.: Observations on the Treatment of Amyotrophic Lateral Sclerosis (Leucopolyomyelopathy) with Vitamin E, *J. Nerv. & Ment. Dis.* **93**:370 (March) 1941.

the reports of others<sup>8</sup> make it clear that the efficacy of the therapy is far from proved.

This report covers a group of 35 patients treated with large doses of synthetic alpha tocopherol, beginning May 1940. The purpose of the study was to follow the course of the patients as objectively as possible. An attempt was made to evaluate their status at frequent intervals, not only by recording the subjective impressions both of the patient and of the physician but by getting a quantitative measurement of progress. There is little objective information available regarding the course of untreated patients with amyotrophic lateral sclerosis, the muscular dystrophies and the muscular atrophies. The measurements made on this series of patients may therefore be of value not only in demonstrating the lack of effectiveness of alpha tocopherol in the treatment of these disorders but in providing an objective observation of the progress of these diseases. Such information may be of value as control data in any future investigation of therapeutic agents in this field.

#### METHOD AND MATERIAL

The following examinations were made:

1. Muscular strength was measured by dynamometric methods, using the ordinary grip dynamometer and a spring balance for the larger muscle groups. All measurements were made in pounds. It should be emphasized that these measurements were all made by the same observer, which eliminated insofar as possible variations in technic.

2. Electric examinations, employing galvanic and faradic currents and chronaxia measurements, were performed on a portion of the patients before the medication was begun and after as long a period as possible. These were made by Dr. W. H. Northway, of the division of physical therapy.

3. Determinations of the creatinine and creatine output in twenty-four hour specimens of urine were made at frequent intervals in those patients, predominantly those with muscular dystrophies, whose creatine metabolism was measurably disturbed. Because of difficulty in regulating the diet, creatine tolerance tests were not feasible.

The patients fell into four groups: (1) 7 with amyotrophic lateral sclerosis; (2) 9 with muscular dystrophy; (3) 5 with muscular atrophy of unknown cause, and (4) 14 with other diseases of the neuromuscular system. The duration of the treatment was from three days, when death ensued, to eleven months. Synthetic alpha tocopherol was administered orally in all cases and parenterally as well in most. In general the dosage employed was significantly higher than that mentioned in any of the published reports. No additional vitamin therapy was used.

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8. Shelden, C. H.; Butt, H. R., and Woltman, H. W.: Vitamin E (Synthetic Alpha-Tocopherol) Therapy in Certain Neurologic Disorders, *Proc. Staff Meet., Mayo Clin.* **15**:577-580 (Sept. 11) 1940. Doyle, A. M., and Merritt, H. H.: Vitamin Therapy of Diseases of the Neuromuscular Apparatus, *Arch. Neurol. & Psychiat.* **45**:672-679 (April) 1941. Denker, P. G., and Scheinman, L.: Treatment of Amyotrophic Lateral Sclerosis with Vitamin E (Alpha-Tocopherol), *J. A. M. A.* **116**:1893-1895 (April 26) 1941. Ferrebee, J. W.; Klingman, W. O., and Frantz, A. M.: Vitamin E and Vitamin B<sub>6</sub>, *ibid.* **116**:1895-1896 (April 26) 1941.

RESULTS

*Group 1. Amyotrophic Lateral Sclerosis.*—CASE 1.—A 42 year old man complained of generalized weakness and dysarthria of six months' duration. There were weakness of all muscle groups, especially of the intrinsic muscles of the hands, and moderate spasticity of the muscles of the legs. Atrophy of the small muscles of the hand and fibrillary twitches in the muscles of both upper extremities, the shoulder girdle and the tongue were observed. All deep reflexes were hyperactive. The Hoffmann reflex was positive bilaterally, and unsustained bilateral patellar and ankle clonus were present.

Treatment: The patient received 300 mg. of alpha tocopherol daily by mouth; in addition he was given 400 mg. intramuscularly daily for three weeks, then 400 mg. intramuscularly at bimonthly and monthly intervals for seven months.

Results: Subjectively he felt some improvement during the first month; even now (June 1941) he appears hopeful. Objectively he has become progressively worse. Muscle tests show decreasing strength; marked jaw clonus has appeared, and dysarthria and dysphagia are severe. Main en griffe deformities are appearing in the hands. Chronaxia readings show that the interosseous muscles of both hands are definitely less excitable to electric stimulation than before the therapy was begun.

Chronaxia Measurements, Sigmas (1 Sigma = 0.001 Second)

Dorsal Interosseus			
Hand	Muscle	Oct. 10, 1940	May 10, 1941
Right	I.....	4.0	8.0
	II.....	0.4	8.0
	III.....	0.4	2.0
	IV.....	0.4	0.8
Left	I.....	8.0	8.0
	II.....	0.4	No contracture
	III.....	0.4	No contracture
	IV.....	0.2	8.0

Excretion of Creatinine and Creatine

	Creatinine, Gm./24 Hr.	Creatine, Gm./24 Hr.
Oct. 10, 1940.....	1.52	None
May 10, 1941.....	1.50	0.030

CASE 2.—A 57 year old man complained of progressive weakness of the hands and arms and cramps in the legs of one year's duration. Examination revealed a global atrophy of the intrinsic muscles of the hands and moderate atrophy of the muscles of the arms, forearms and shoulder girdle. Fibrillary twitches were present in the arms and calves. The tendon reflexes were hyperactive; sustained ankle clonus was present on the left side and unsustained ankle clonus on the right side; moderate spasticity of the legs was present.

Treatment: For four months he received 100 mg. of alpha tocopherol intramuscularly every week and 50 mg. orally every day. During the succeeding six months he had no therapy. For one month he then was given 250 mg. orally each day.

Results: He now (May 1941) expresses the belief that he has become progressively worse since the institution of the therapy. The results of neurologic examination are essentially the same except that the Hoffmann sign is now positive on the right side and there has been some increase in the atrophy. During

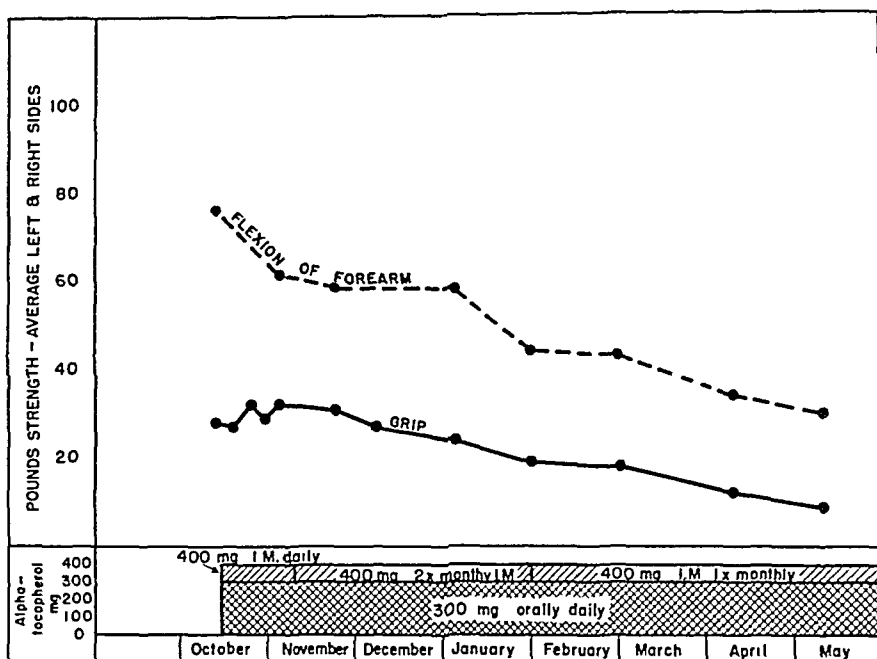


Fig. 1 (group 1, case 1).—A 42 year old man. His strength became progressively weaker after the institution of therapy with alpha tocopherol.

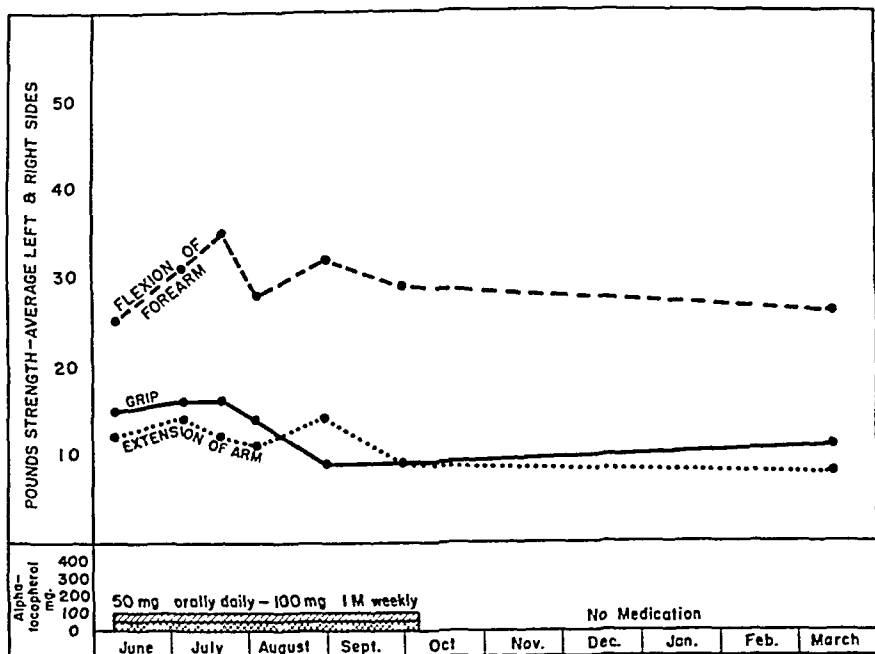


Fig. 2 (group 1, case 2).—A 57 year old man. The muscle measurements remained almost stationary independent of the administration of alpha tocopherol.

the six months in which he was taking no alpha tocopherol his muscular strength remained about stationary.

**CASE 3.**—A 59 year old man complained of progressive generalized weakness, clumsiness and stiffness of the hands, dysphagia and dysarthria of at least four months' duration. Examination showed generalized atrophy, especially in the hands, weakness of the facial muscles and fibrillations over the entire body and in the tongue. The tendon reflexes were all quite active, but no pathologic reflexes were present. There was definite mental deterioration.

**Treatment and Results:** For three days he was given 50 mg. of alpha tocopherol orally and 100 mg. intramuscularly. He died on the fourth day after the medication was started.

**CASE 4.**—A 52 year old woman had noted cramplike pains in the thighs and calves for about three years. These were followed by difficulty in walking. Six

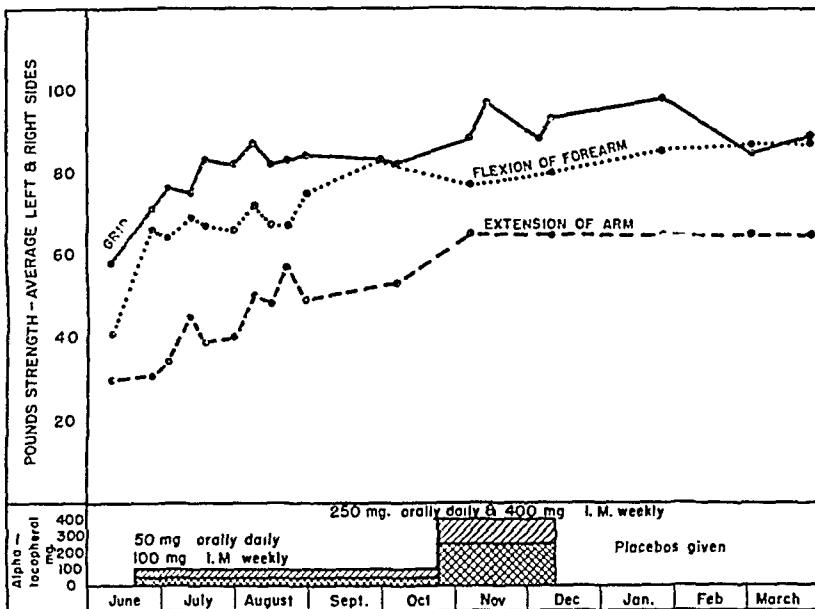


Fig. 3 (group 1, case 5).—A 40 year old man. He improved greatly during the administration of alpha tocopherol; the improvement was sustained when placebos were administered.

months previously she had begun to notice weakness of the arms. Examination showed generalized muscular weakness; extensive fibrillary twitchings in the tongue, shoulder girdle, arms and thighs; dysphagia and dysarthria and wasting of the interosseus spaces and of the thenar eminences. The tendon reflexes were definitely hyperactive, although no pathologic reflexes were elicited.

**Treatment and Results:** She received 100 mg. of alpha tocopherol intramuscularly three times a week and 50 mg. orally every day from May 21 until Sept. 1, 1940, when she entered the hospital unable to speak and breathing with difficulty. She died several hours later. Autopsy revealed typical changes of amyotrophic lateral sclerosis with involvement of the motor nuclei of the bulb.

**CASE 5.**—A 40 year old man had noted weakness and an "itching" sensation in the left arm after an attack of swelling in that arm two years previously. Examination revealed that wasting of the arm and shoulder girdle and some

fibrillary twitches were present on the left side. The Hoffmann reflex was positive bilaterally, and the tendon reflexes were quite active in the arms. No other pathologic reflexes were present. The legs were normal. A positive Wassermann reaction of the blood was discovered when his arm became swollen, and he has received intermittent antisyphilitic therapy (bismuth and arsenic compounds) since that time. In November 1939 his blood gave a 3 plus Wassermann reaction; in July 1940 the reaction had become negative. An examination of the spinal fluid in November 1938 yielded nothing abnormal. The diagnosis of amyotrophic lateral sclerosis was, of course, tenuous in this case because of the history of syphilis and because of the atypical clinical picture. However, it was felt that this was a possibility because of the downhill course of the patient's illness in spite of therapy with heavy metal compounds.

**Treatment:** He was given 50 mg. of alpha tocopherol orally each day and 100 mg. intramuscularly each week for four months, then 250 mg. orally every day and 400 mg. intramuscularly every week for one and a half months. During the five months since that time he has received both oral and parenteral placebos. He has also received either a bismuth preparation or neoarsphenamine during the entire eleven months.

**Results:** There has been marked improvement since the institution of the therapy. The fibrillations have disappeared; he is less clumsy, and dynamometric readings have shown a definite increase. The increase in the dosage of the alpha tocopherol and subsequently the use of placebos had no effect on the course of his illness. The Hoffmann reflexes have remained.

#### Excretion of Creatinine and Creatine

	Creatinine, Gm./24 Hr.	Creatine, Gm./24 Hr.
June 13, 1940.....	1.500	0.188
June 14 .....	Medication started	
August 29 .....	0.936	0.038
September 30 .....	0.860	0.159
October 15 .....	Placebos started	
Feb. 27, 1941.....	1.160	0.000
April 15 .....	1.118	0.047

**CASE 6.**—A 66 year old man had noted during the preceding five months that his right arm and hand were becoming weak and wasted and during the past week that his right leg was also weak. Atrophy was present at numerous sites bilaterally but was most marked in the interosseous muscles and the thenar and hypothenar eminences of the right hand, in the triceps muscle and in the supra-scapular and subscapular groups of muscles on the right side. Fibrillary twitchings were present throughout the body, including the tongue. The muscles of the right leg were spastic. The deep reflexes were all hyperactive. The Babinski reflex was positive on the right side, and the Chaddock reflex was positive on the left side. The Hoffmann reflex was positive bilaterally.

**Treatment:** He has been given alpha tocopherol for eleven months. During the first four months he received 100 mg. intramuscularly three times weekly and 50 mg. orally every day. Since that time he has received 400 mg. intramuscularly three times weekly and 250 mg. orally each day.

**Results:** Unfortunately it was not possible to follow this patient with quantitative muscle measurements. However, it is evident to all, including his family, that he has become worse. There is considerable increase in his weakness, and severe dysarthria and dysphagia are present.



CASE 7.—A 48 year old woman complained of progressive weakness of the left arm and hand following an attack of influenza six weeks previously; she also noted that the muscles "jumped." In addition, she had had progressively more difficulty in speaking and occasional trouble in breathing. Generalized weakness was present. Atrophy and occasional fibrillations were seen in both hands, especially the left. There were moderate dysarthria and fibrillations of the tongue. The tendon reflexes were all active, and the left knee jerk was greater than the right. The Babinski, Oppenheim and Gordon reflexes were positive on the left side.

Treatment: She was given 250 mg. of alpha tocopherol orally and 400 mg. intramuscularly every day for the first eleven days. During the past fourteen weeks she received 300 mg. orally every day and had three 400 mg. injections.

Results: She stated after the first week of therapy that "all the weakness is going away." On recent visits to the clinic, however, she has become discouraged

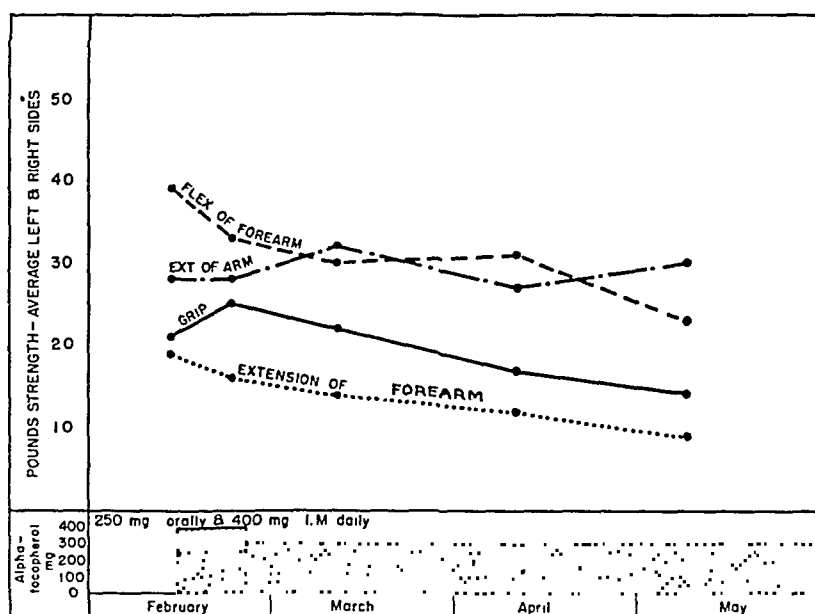


Fig. 4 (group 1, case 7).—A 48 year old woman. Her condition became progressively worse. She received three 400 mg. injections of alpha tocopherol during March, April and May in addition to the 300 mg. oral daily dose indicated in the chart.

and expressed the belief that she is much worse; this is verified by measurements of muscle strength. Her weakness, dysarthria, dysphagia and dyspnea have increased. Chronaxia measurements made on May 8, 1941, are the same as those made on February 12, except that responses could no longer be obtained from the second, third and fourth dorsal interosseous muscles and the abductor minimi digiti on the left side.

#### Excretion of Creatinine and Creatine

	Creatinine, Gm./24 Hr.	Creatine, Gm./24 Hr.
Feb. 11, 1941.....	0.708	0.027
May 8 .....	0.745	0.048

Summary: Six patients with the classic form of amyotrophic lateral sclerosis were treated; in all of them the Aren-Duchenne type of atrophy of the small muscles of the hand was present, in addition to signs of involvement of the pyramidal tract both in the upper and in the lower extremities and fibrillations. The illness of all of these patients has taken a progressive downhill course: Two have died; 3 are in a critical condition, and 1 is definitely worse than prior to the institution of the therapy. One other patient (case 5), whose condition was diagnosed as possible amyotrophic lateral sclerosis in the presence of a positive Wassermann reaction of the blood and an atypical clinical picture, was markedly improved after treatment with both alpha tocopherol and heavy metal compounds. This improvement continued unabated during

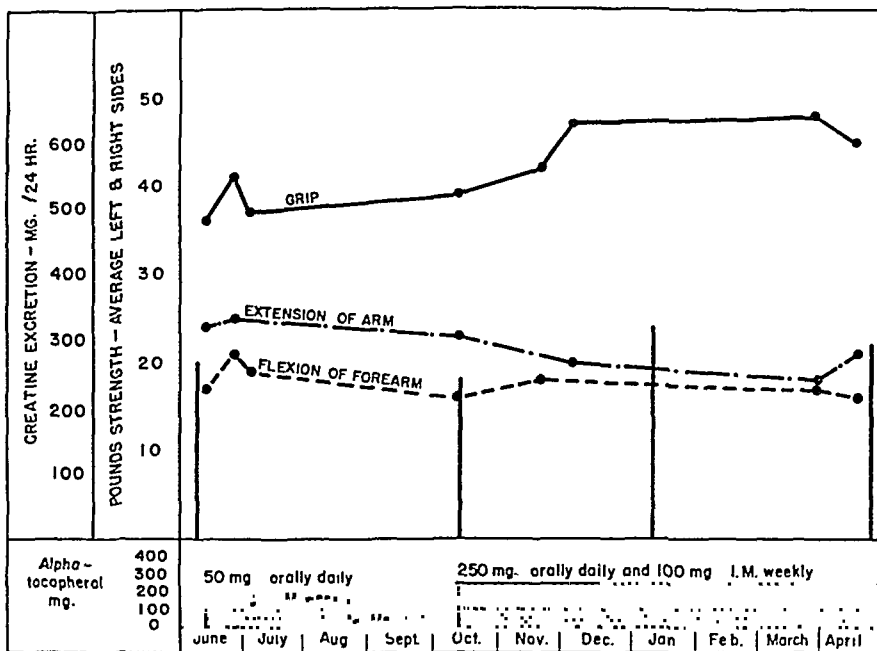


Fig. 5 (group 2, case 1).—An 18 year old woman. No change was noted in her condition. The vertical lines represent creatine excretion.

a five month period in which placebos were substituted for the vitamin, and therefore it could not be attributed to the alpha tocopherol.

*Group 2. Muscular Dystrophy.*—CASE 1.—An 18 year old woman had noted weakness, waddling and difficulty in climbing since early childhood. Her condition appeared to be a typical example of the pseudohypertrophic type of muscular dystrophy, with large, rounded calves. The deep reflexes were hypoactive or absent.

Treatment: Alpha tocopherol in daily oral doses of 50 mg. and weekly intramuscular doses of 100 mg. was given for two months. The patient received no medication during the following two months. She then was given 250 mg. of the vitamin orally each day and 100 mg. intramuscularly every week for seven months.

Results: She expresses the belief that she has felt stronger since beginning the therapy. Her gait, however, appears the same as formerly, and muscle

measurements remain essentially constant. The abnormality in muscle metabolism as shown by the excretion of creatinine and creatine remains the same.

### Excretion of Creatinine and Creatine

	Creatinine, Gm./24 Hr.	Creatine, Gm./24 Hr.
July 2, 1935.....	0.503	0.284
June 8, 1940.....	0.636	0.287
June 12 .....	Medication started	
August 3 .....	0.909	0.00
August 14 .....	Medication stopped	
October 11 .....	0.617	0.279
October 12 .....	Medication started	
Jan. 10, 1941.....	0.819	0.306
April 18 .....	0.609	0.295

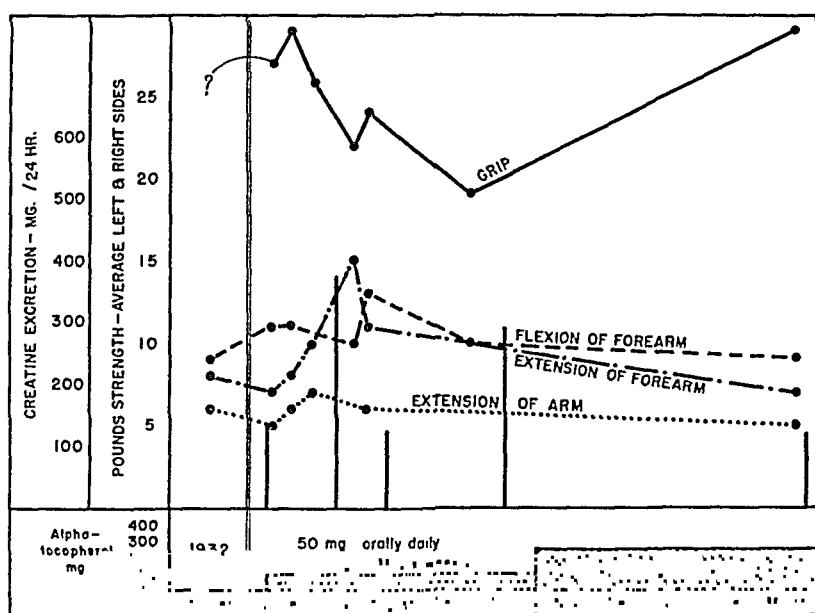


Fig. 6 (group 2, case 2).—A 50 year old man. No change was noted in his condition. The dynamometric measurements of 1932 were almost identical with those of 1940-1941. The variations in creatine excretion, commonly seen, were due to changes in diet, etc., and showed no uniform trend.

CASE 2.—A 50 year old man complained of weakness which had been present since he was 15 years old, most marked in the thighs. He had a typical dystrophic gait and stance. Marked weakness of all muscle groups was present, and all of the deep reflexes were absent.

Treatment: He received 50 mg. of alpha tocopherol orally every day and 100 mg. intramuscularly twice a week for four and a half months and then 250 mg. orally every day for seven months.

Results: He is optimistic and feels that he is improving; this same optimism has been present with numerous other types of medication, including sterile solution of sodium chloride, given since 1932. His condition remains stationary as judged by objective methods.

## Excretion of Creatinine and Creatine

	Creatinine, Gm./24 Hr.	Creatine, Gm./24 Hr.
June 8, 1940.....	0.529	0.124
June 11 .....	Medication started	
July 15 .....	0.814	0.378
September 10 .....	0.552	0.117
October 14 .....	0.611	0.285
March 24, 1941.....	0.568	0.109
May 6 .....	1.060	0.120

CASE 3.—A 6 year old boy complained of trouble in walking and weakness of several years' duration. The most marked weakness was in the muscles of the shoulder girdle, trunk and thighs. There was a lumbar lordosis. The ankle jerks were the only deep reflexes elicited.

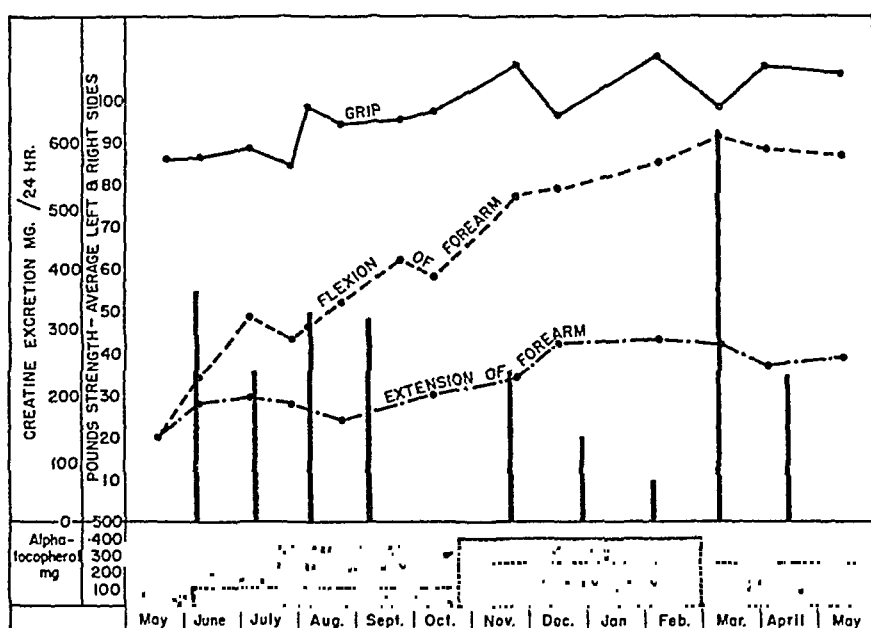


Fig. 7 (group 2, case 4).—A 53 year old man. A progressive increase in strength was noted during the first six months of therapy with alpha tocopherol, but during the last six months his condition became stationary and a waddling gait remained. Creatine excretion remained abnormal even during clinical improvement. It was felt that this improvement preceded the administration of the vitamin, but no measurements were taken at this time.

Treatment: He was given 100 mg. of alpha tocopherol intramuscularly three times a week and 50 mg. orally every day for six months.

Results: Although it was impossible to obtain his cooperation in performing quantitative muscle tests or collecting specimens of urine for studies of the excretion of creatinine and creatine, it was felt that he was somewhat worse after receiving the medication.

CASE 4.—A 53 year old man noted weakness of the arms, difficulty in walking and loss of 12 pounds (5.4 Kg.) in weight during the preceding one and a half years. His gait was waddling, and he was unable to arise from a chair without assistance. During the month preceding medication with alpha tocopherol it was

noted both by the patient and by his physician that his gait was improving, his strength seemed to be increasing and he was able to arise from a chair without assistance.

**Treatment:** He was given 50 mg. of alpha tocopherol orally every day and 100 mg. intramuscularly three times weekly for four and a half months, 250 mg. orally every day and 400 mg. intramuscularly three times a week for four months and 250 mg. orally each day for two and a half months.

**Results:** Definite improvement was noted during the first six months after the medication was begun; no improvement was noted during the last six months. The patient expresses the belief that the rate of improvement was not increased after he started to take the medicine, although no muscle measurements were taken during the period prior to medication. A rather marked waddling gait still remains. The excretion of creatinine and creatine also remains as abnormal as ever.

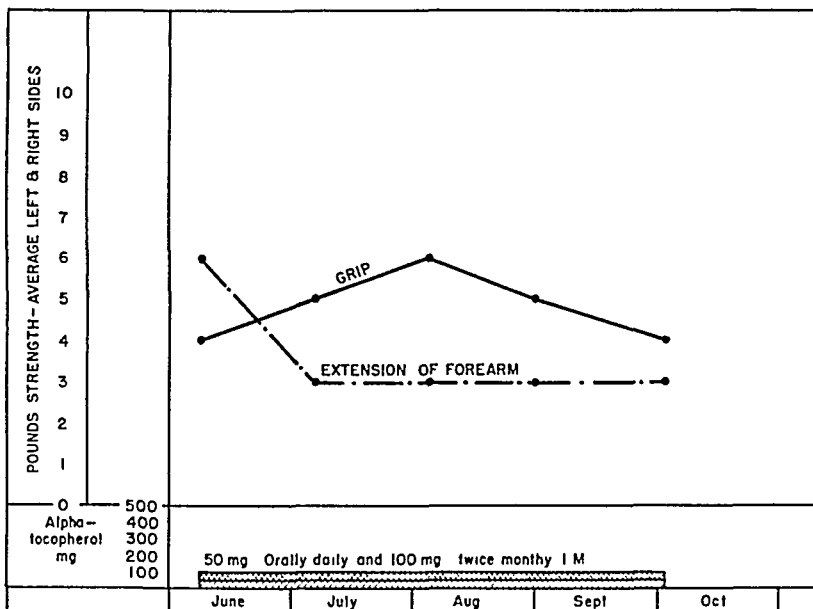


Fig. 8 (group 2, case 5).—A 17 year old youth. No change was noted in his condition.

#### Excretion of Creatinine and Creatine

	Creatinine, Gm./24 Hr.	Creatine, Gm./24 Hr.
April 16, 1939 .....	1.16	0.00
June 7, 1940 .....	0.947	0.359
June 13 .....	Medication started	
July 8 .....	0.997	0.225
August 6 .....	1.078	0.322
September 12 .....	0.822	0.313
November 22 .....	0.918	0.278
December 30 .....	0.999	0.135
Feb. 4, 1941 .....	1.020	0.076
March 20 .....	0.612	0.612
April 17 .....	1.048	0.223

**CASE 5.**—A 17 year old boy complained of weakness of about twelve years' duration, progressive until five years ago. He had a half-brother with a similar

disorder. His entire musculature was wasted, and he was unable to stand. His deep reflexes were absent; there were no fibrillations.

Treatment: He was given 50 mg. of alpha tocopherol orally every day and 100 mg. intramuscularly once every two weeks for four months.

Results: No change has been observed in his condition except that he expresses the belief that he has more "pep."

CASE 6.—A 35 year old man stated that generalized weakness and difficulty in walking had appeared during the preceding seven years. He was thin and rather wasted, with a waddling gait. His biceps and some of the muscles of his leg, especially his anterior tibial muscles, were atrophic. The deep reflexes were difficult to elicit.

Treatment: He received 250 mg. of alpha tocopherol orally every day and 400 mg. intramuscularly every week for six months.

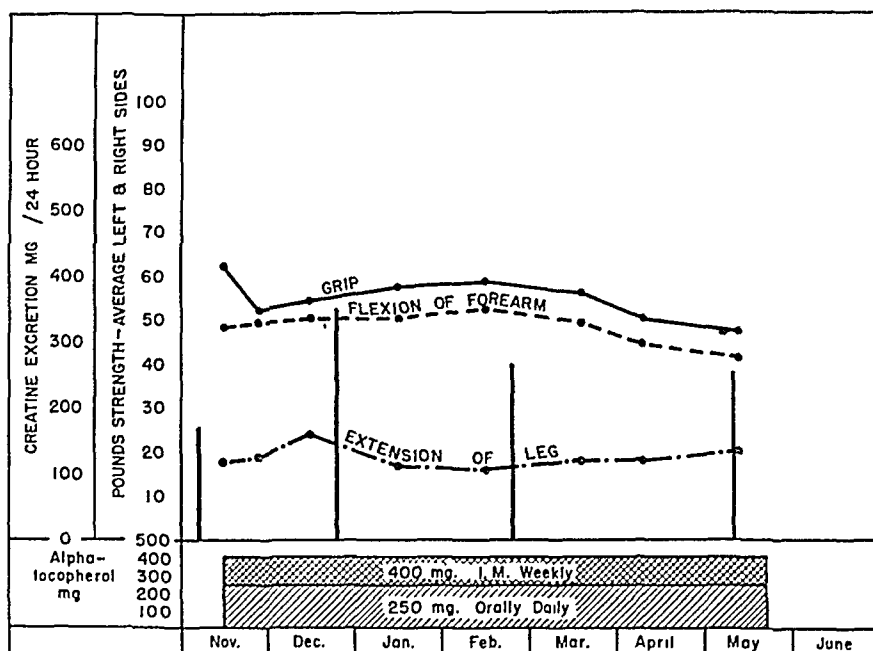


Fig. 9 (group 2, case 6).—A 35 year old man. No change was noted in his condition.

Results: While his gait and muscular strength appeared the same to the examiner, the patient expresses the belief that his arms are stronger and that he stumbles less than he did prior to the medication. This testimony is controverted by the measurements of muscle strength, the continued appearance of large amounts of creatine in the urine and the electric reactions, which did not change during medication.

#### Excretion of Creatinine and Creatine

	Creatinine, Gm./24 Hr.	Creatine, Gm./24 Hr.
Jan. 11, 1935 .....	0.866	0.067
Nov. 6, 1940 .....	0.494	0.174
Nov. 19 .....	Medication started	
December 26 .....	0.548	0.355
Feb. 26, 1941 .....	0.488	0.262
May 7 .....	0.372	0.257

CASE 7.—A 31 year old man had difficulty in climbing which he had first noted about thirteen years ago. He had gradually become weaker since that time. He was able to rise from a chair with difficulty. He stated that his muscles increased in size during the first years of his illness but that recently they became smaller. His gait was waddling; lumbar lordosis was present, and the deep reflexes were absent. He has a brother with the same difficulty.

Treatment: He received 250 mg. of alpha tocopherol orally every day and 200 mg. intramuscularly every week for four months.

Results: He states that he "may" be a little stronger. To the observer, however, his gait and strength are apparently unchanged.

#### Excretion of Creatinine and Creatine

	Creatinine, Gm./24 Hr.	Creatine, Gm./24 Hr.
Feb. 4, 1941 .....	0.810	0.470
February 5 .....	Medication started	
February 28 .....	0.949	0.110
April 14 .....	0.752	0.024
May 26 .....	0.744	0.217
May 27 .....	0.432	0.196

CASE 8.—A 31 year old man had noted since the age of 10 that he could not run as well as his classmates. During the past three years the difficulty had become so much more marked that he could climb stairs only with great effort. His gait was not greatly impaired; however, there was a mild but definite waddle. Atrophy was not present.

Treatment: He received 250 mg. of alpha tocopherol orally every day and 400 mg. intramuscularly every week for six months.

Results: The patient can detect no difference in his strength or gait. Muscle measurements made on May 10, 1941, compared with those made on Nov. 9, 1940, showed a mild decrease in strength.

#### Excretion of Creatinine and Creatine

	Creatinine, Gm./24 Hr.	Creatine, Gm./24 Hr.
Nov. 2, 1940 .....	0.665	0.093
November 9 .....	Medication started	
May 11, 1941 .....	0.890	0.089

CASE 9.—A 9 year old boy complained of progressive difficulty in walking of four years' duration and presented the typical picture of pseudohypertrophic muscular dystrophy, with a waddling gait, generalized weakness, lumbar lordosis and well rounded muscles of the calves. He had been treated during the preceding five months with one teaspoon of wheat germ oil daily, and his parents felt that he was getting worse during this period.

Treatment: He received 250 mg. of alpha tocopherol orally every day for four weeks.

Results: To date there has been no significant change in measurements of muscle strength.

#### Excretion of Creatinine and Creatine

	Creatinine, Gm./24 Hr.	Creatine, Gm./24 Hr.
April 24, 1941 .....	0.298	0.450
April 25 .....	Medication started	
May 8 .....	0.198	0.293
May 22 .....	0.220	0.292

Summary: Eight patients with muscular dystrophy were treated with alpha tocopherol for an average of seven and three-tenths months. One other patient (case 9) was observed for only four weeks; he had, however, received wheat germ oil for five months previously, with continued progress of the disease. Only 1 patient showed definite objective improvement (case 4), and he was a man whose illness began at the age of 51, an unusually late onset. This improvement, which was only moderate in degree, definitely began before the therapy was started and continued only during the early part of it. In no case, including this one, did the abnormal muscle metabolism, as measured by determination of the excretion of creatinine and creatine in the urine, revert to normal.

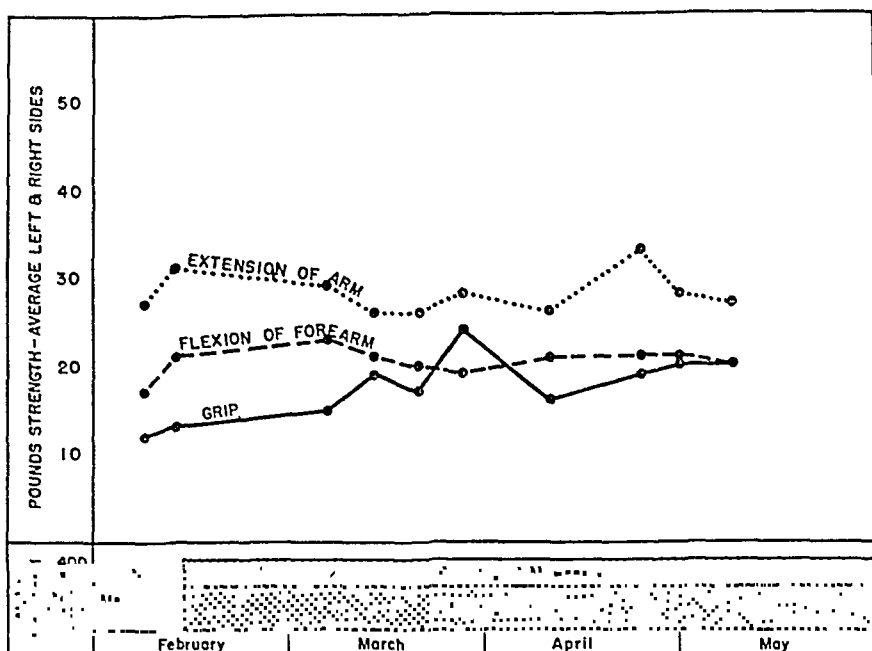


Fig. 10 (group 3, case 1).—A 60 year old woman. There was no change in her condition except for the apparent increase in the strength of her grip. The variation in the dynamometric readings before the administration of the vitamin E should be noted.

*Group 3. Muscular Atrophies.*—CASE 1.—A 60 year old woman complained of gradually progressing weakness, most marked in the hands, of one and a half years' duration. There was marked atrophy of all of the intrinsic musculature of both hands, and a few fibrillary twitches were seen in the muscles of the forearms and hands. All deep reflexes were absent except the knee jerks.

Treatment: She received 250 mg. of alpha tocopherol orally every day and 400 mg. intramuscularly every week for four months.

Results: She expresses the belief that she has improved "a little." Muscle measurements have remained essentially constant except for a slight increase in the strength of the grip on the left side.

CASE 2.—A 57 year old man had noticed weakness of the right hand of one year's duration; more recently moderate weakness of the left hand has appeared.



Global atrophy of the musculature of both hands was noted, most marked on the left side. Fibrillary twitches were observed in the interosseous muscles and in the muscles of the forearm.

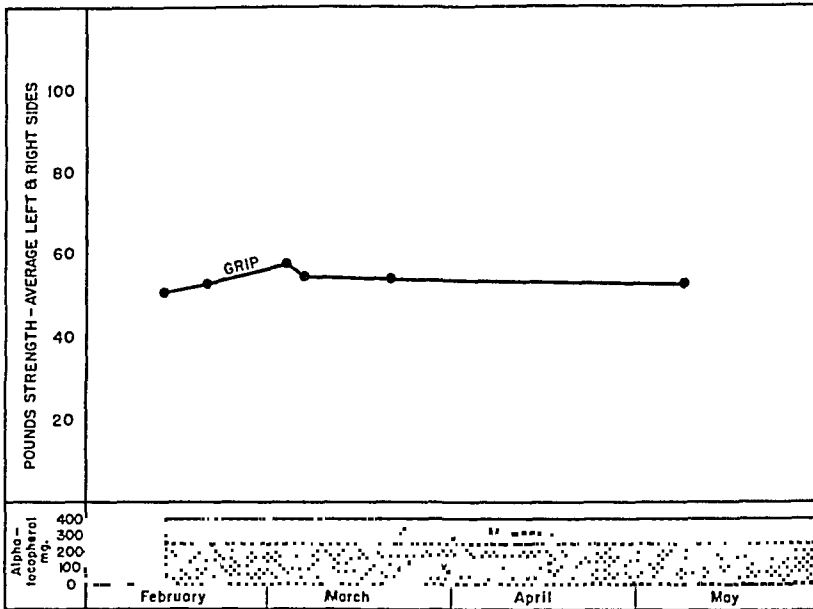


Fig. 11 (group 3, case 2).—A 57 year old man. No change was noted in his condition.

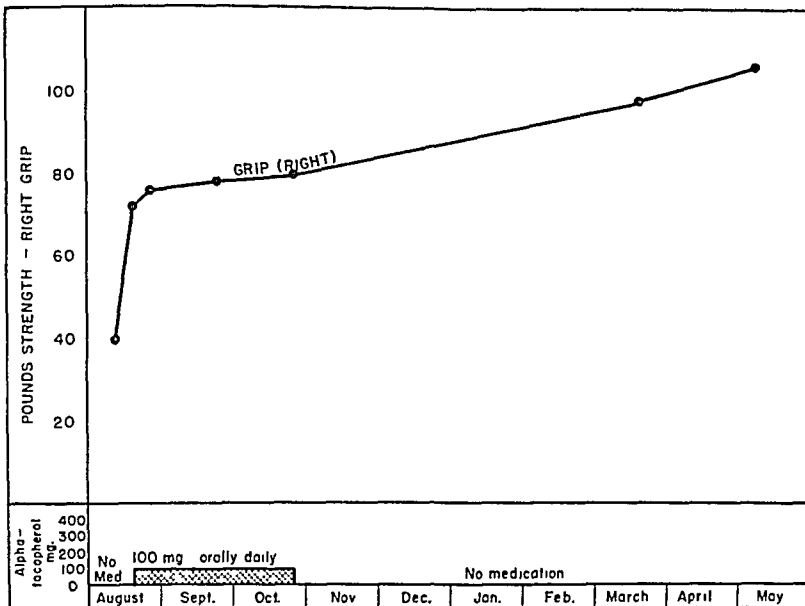


Fig. 12 (group 3, case 3).—A 42 year old man. Marked improvement in his condition was noted. However, the initial rise in strength (from 42 to 72 pounds [19.1 to 32.7 Kg.]) preceded the administration of alpha tocopherol, and the improvement continued after its cessation.

Treatment: He received 250 mg. of alpha tocopherol daily by mouth and 400 mg. intramuscularly every week for four months.

Results: Measurements of the strength of his grip show no appreciable change. Fibrillations, if anything, are more numerous than before. Chronaxia readings made on Feb. 18 and April 24, 1941, were essentially the same; both first dorsal interosseous muscles had a prolonged stimulation time.

CASE 3.—A 42 year old man had noted a gradually progressing atrophy of the intrinsic muscles of the right hand and inability to abduct the right fifth finger since he had bruised the palm of his right hand four months previously. No atrophy was discernible on the left side. All types of sensation were normal. The deep tendon reflexes were active. A two week period of observation prior to the administration of the vitamin revealed an increase in strength during this time.

Treatment: A dose of 100 mg. of alpha tocopherol was administered daily for two months.

Results: The improvement continued, and finer movements of the hands were performed better than previously. After the medication was stopped the improvement continued, so that after five months without any therapy the atrophy had largely disappeared and the patient's hand seemed about normal. Electric reactions of the dorsal and volar interosseous muscles, the abductor minimi digiti quinti and the first and second lumbrical muscles, which had shown a partial reaction of degeneration on Aug. 26, 1940, were normal on April 21, 1941. The adductor pollicis did not respond to the faradic current at the time of either examination.

CASE 4.—A 54 year old man complained of slowly progressive weakness, especially noted in the legs, that had begun at least ten years previously. Generalized wasting of the legs was present; there was bilateral foot drop, which was worse on the left side. No fibrillations were seen. The knee and ankle jerks were absent.

Treatment: He was given 50 mg. of alpha tocopherol orally every day and 100 mg. intramuscularly every week for five months and 250 mg. orally every day and 400 mg. intramuscularly every week for six months.

Results: The patient states that his "general condition" is better, but the dynamometric readings show that his strength has remained constant. He has also continued to excrete rather large amounts of creatine in his urine. Electric examinations on May 14, 1940, and April 21, 1941, revealed no change except that the extensor digitorum longus, which had responded both to faradic and to galvanic current at the first examination, failed to respond to either during the latter one.

#### Excretion of Creatinine and Creatine

	Creatinine, Gm./24 Hr.	Creatine, Gm./24 Hr.
June 6, 1940.....	0.894	0.073
June 14 .....	Medication started	
July 18 .....	1.030	0.183
August 20 .....	1.070	0.434
October 7 .....	1.210	0.141
November 12 .....	1.308	0.097
March 5, 1941.....	1.20	0.337
April 17 .....	0.807	0.271

CASE 5.—A 48 year old man complained of progressive weakness and wasting of the left hand of two years' duration. There were marked atrophy of the first dorsal interosseous muscle and moderate atrophy of the other interosseous

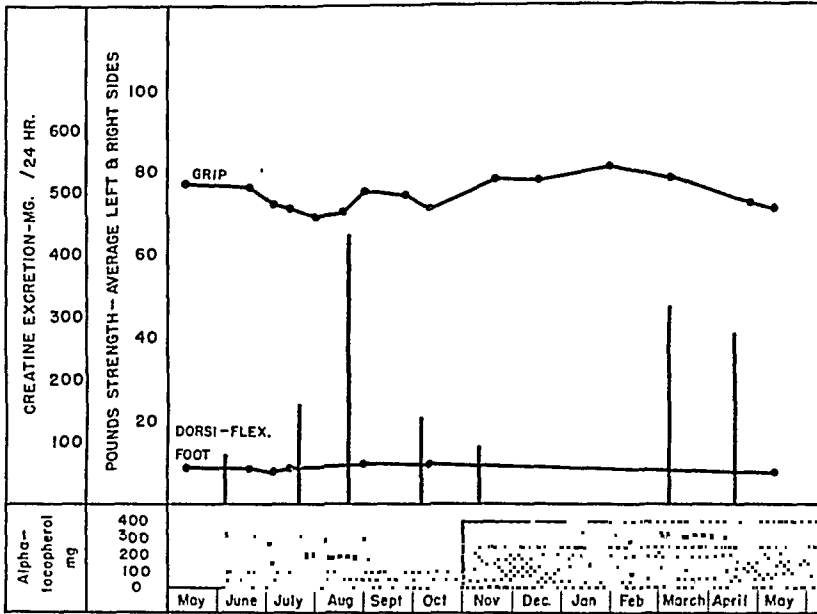


Fig. 13 (group 3, case 4).—A 54 year old man. No change was noted in his condition.

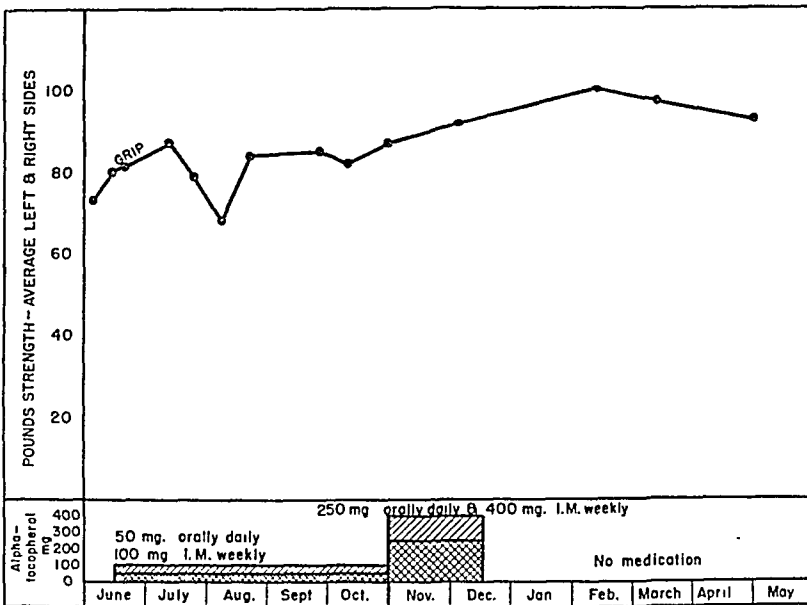


Fig. 14 (group 3, case 5).—A 48 year old man. Definite improvement was noted during the administration of the vitamin; the improvement continued after it was stopped.

muscles on the left side. Questionable atrophy of the muscles of the right hand was noted. There were no sensory changes, although the patient complained of numbness of the left hand. No fibrillations were seen; the deep reflexes were

present. He drank a considerable amount of alcohol and was a poor eater when first seen, and it was felt that alcohol, avitaminosis and possibly lead may have contributed to his condition.

Treatment: He received 50 mg. of alpha tocopherol orally every day and 100 mg. intramuscularly every week for four and a half months and 250 mg. orally every day and 400 mg. intramuscularly every week for one and a half months; no alpha tocopherol therapy was given during the past five months.

Results: There was definite improvement in strength during therapy; this improvement has continued during the six months since the therapy was stopped. At present only a mild degree of atrophy is noted in the first dorsal interosseus muscle on the left side. All electric reactions are normal, in contrast to a partial reaction of degeneration which was present in the first dorsal interosseus muscle and the second lumbrical muscle on the left side and in the volar interosseous muscles on both sides.

Summary: Five patients with muscular atrophy of unknown origin were treated from two to eleven months, for an average of five months. Definite improvement was noted in 2 of them (cases 3 and 5). In the first of these the atrophy was restricted to one hand and, curiously enough, began after local trauma. Improvement probably began preceding the treatment and continued five months after it was discontinued. In the other case the possible etiologic relation of alcohol, avitaminosis and lead was questioned before the therapy was started; further improvement was noted for more than five months after its discontinuance. The other 3 patients did not improve.

Case 4 is unusual in that large amounts of creatine (from 0.097 to 0.434 Gm. per twenty-four hours) were excreted. In my experience excretion of more than 0.100 Gm. per twenty-four hours is uncommon in the spinal amyotrophies in contrast to its frequent occurrence in the muscular dystrophies. Perhaps the condition in this case is related to the latter ones, although the distal type of myopathy (Gowers) is a rare and often questioned type of dystrophy.

*Group 4. Other Diseases of the Neuromuscular System.*—The following other diseases were treated with alpha tocopherol: multiple sclerosis (4 cases), syphilitic amyotrophy (1 case in which the classic picture of amyotrophic lateral sclerosis was presented and 1 case of rapidly progressing bulbar palsy with widespread atrophy and fibrillations), posterolateral sclerosis of unknown origin (2 cases), amyotonia congenita (1 case), myotonia dystrophica (1 case), "lateral sclerosis" (?) (1 case), atrophy probably following poliomyelitis (1 case), fibrillations and weakness in a debilitated woman and fibrillations and weakness in the hands of a woman with rheumatoid arthritis.

In all of the cases of multiple sclerosis the patients exhibited both remissions and subsequent exacerbations during the course of treatment.

One of the patients with syphilitic amyotrophy did not improve with combined alpha tocopherol and antisyphilitic therapy; the other died, and autopsy revealed the pathologic changes characteristic of syphilitic meningomyelitis. In all of the other cases the condition remained stationary during the period of therapy.

#### COMMENT

No patient with amyotrophic lateral sclerosis, muscular dystrophy, muscular atrophy or other neuromuscular disease showed any definite improvement, as measured mechanically, electrically or chemically, that could be directly attributed to the use of large amounts of alpha tocopherol. While it is true that 4 of the 35 patients did recover more or less function, these improvements either preceded the medication or were sustained when placebos were given or when medication was withheld. Many of the patients who showed no objective improvement, it should be noted, stated during some part of the treatment period that they considered themselves to be benefited. Such statements could easily be interpreted as significant if quantitative methods were not employed in measuring muscle strength.

While Bicknell, Wechsler and Stone used the vitamin B complex and either whole wheat germ or wheat germ oil as a supplementary agent, it is difficult to believe that this alone is responsible for the divergence of results, inasmuch as most of the present group were on entirely adequate diets.

Of interest is the fact that 10, or 50 per cent, of the patients in the 20 cases classified by Wechsler as instances of amyotrophic lateral sclerosis were women and that 5 of the 6 patients said to be markedly improved or recovered were women in the "premenopausal" age group. This is in marked contrast to the experience of others, who have noted that amyotrophic lateral sclerosis occurs at least four times as frequently in men as in women (according to Wilson,<sup>9</sup> the patients were women in 59 of 72 cases reported by Dana and in 84 of 99 cases reported by Roberts). Such a distribution makes it seem reasonable to question whether the conditions in the cases reported by Wechsler were similar to those ordinarily classed as amyotrophic lateral sclerosis.

The reported improvements are particularly difficult to explain in view of the observation of Einarson and Ringsted<sup>2</sup> that the parietic condition in rats, which they asserted was comparable to amyotrophic lateral sclerosis, was not "cured" but that the animals merely did not become worse. So even if one admits the similarity of the disorders, the improvement is still not explainable except that it is due to the suggestive effect of a new therapeutic agent. The explanation of how deficiency of a single vitamin could be responsible for such different

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9. Wilson, S. A. K.: *Neurology*, Baltimore, Williams & Wilkins Company, 1940, p. 1008.

clinical entities as muscular dystrophy, on the one hand, and amyotrophic lateral sclerosis, on the other, is also obscure.

Studies of the excretion of creatinine and creatine in the urine were made on 11 patients having an abnormal output. It was demonstrated that the administration of alpha tocopherol did not effect the excretion of these substances, confirming the work of Fleischmann,<sup>10</sup> who was unable to influence the output in 2 cases of dystrophy and 1 case of amyotonia congenita in which the vitamin was administered. This is in striking contrast to the report of MacKenzie and McCollum,<sup>11</sup> who showed that the creatine excreted in the urine of rabbits on a vitamin E deficient diet rose from less than 10 mg. daily to an average of 80 mg. daily during the occurrence of severe dystrophy and that the increased creatine output fell to a normal level within a few days after vitamin therapy was instituted. This suggests, as Fleischmann pointed out, "a fundamental difference between nutritional muscular dystrophy in rabbits and progressive muscular dystrophy, amyotonia congenita and similar neuromuscular disturbances in human beings."

#### SUMMARY

A group of 35 patients with various disorders of the neuromuscular system were treated with large doses of alpha tocopherol. This group consisted of (1) 7 patients with amyotrophic lateral sclerosis, (2) 9 patients with muscular dystrophy, (3) 5 patients with muscular atrophy of unknown origin and (4) 14 patients with other diseases of the neuromuscular system.

Most of the patients were followed at intervals by (1) measurements of muscular strength by dynamometric methods, (2) electric examinations and (3) measurements of the creatinine and creatine output in the urine.

The conditions of 31 patients remained stationary or became worse during the period of medication. It was shown for the remaining 4 patients, who improved in varying degrees, that the alpha tocopherol probably was in no way responsible for the improvement.

In view of the lack of response to the alpha tocopherol, the repeated observations of muscular strength, electric reactions and excretion of creatinine and creatine may constitute useful data concerning the course of the diseases studied.

Drs. Arthur L. Bloomfield and Henry W. Newman contributed advice during the course of the study and the preparation of the paper.

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10. Fleischmann, W.: Creatine-Creatinine Excretion in Neuromuscular Disease Treated with Alpha-Tocopherol and with Testosterone, *Proc. Soc. Exper. Biol. & Med.* **46**:94-97 (Jan.) 1941.

11. MacKenzie, C. G., and McCollum, E. V.: The Cure of Nutritional Muscular Dystrophy in the Rabbit by Alpha-Tocopherol and Its Effect on Creatine Metabolism, *J. Nutrition* **19**:345-362 (April) 1940.

# Progress in Internal Medicine

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## BLOOD

A REVIEW OF THE RECENT LITERATURE

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To remain informed of medical progress in the face of restrictions of time and facilities imposed by the exigencies of war becomes increasingly difficult for many physicians. We believe that it is the function of a review of current literature to contribute to the correction of this deficiency, and in recognizing the responsibility entailed we are decidedly aware of our shortcomings. This year an attempt has been made to enlarge the scope of the review, but whatever has been gained in comprehensiveness has required some sacrifice of completeness. For omissions both of intent and of oversight we sincerely apologize.

It is hoped that the innovation of a table of contents will increase the accessibility of the material, but it should be remembered that many of the topics considered are not sharply differentiated and that various aspects of a subject may be discussed under several headings.

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From the Thomas Henry Simpson Memorial Institute for Medical Research,  
University of Michigan.

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## PERNICIOUS ANEMIA AND RELATED MACROCYTIC ANEMIAS

The literature of the past year dealing with pernicious anemia is concerned largely with a continuation of attempts to produce the disease experimentally and efforts to define more clearly the relation of the stomach, the liver, the bone marrow, *Diphyllobothrium latum* infection and vitamin deficiencies to the anemia and to the associated lesions of the nervous system. Studies have been made which confirm conclusively the experience that administration of liver extract by intramuscular injection is the most effective type of therapy both for the anemia and for the neurologic manifestations of the disease.

*Etiology.*—In a stimulating article Cooley<sup>1</sup> devotes a brief, but at the same time all-inclusive, paragraph to the subject of heredity in pernicious anemia. He agrees that there is ample evidence of a high incidence of the disease in certain families, indicating that a hereditary factor must be present. Achlorhydria is common in these families and possibly with it a lack of Castle's intrinsic factor. Idiopathic hypochromic anemia is associated with this type of heredity, and it may coexist with pernicious anemia in the same families and even in the same patient. Cooley believes that the incidence of gastric cancer is suspiciously high in the families of patients with pernicious anemia. He suggests that one may choose between several theories, including either that of inherited gastric inferiority, with resultant susceptibility to environmental factors, or the belief that the same mutant gene is responsible for microcytic or macrocytic anemia and specific changes in the nervous system, depending on environmental circumstances. Finally, he makes the rather "timid suggestion" that two genes may be involved, one affecting the stomach and the other the bone marrow. According to him, there is not much doubt that anacidity and probably a diminution of the intrinsic factor are often hereditary precursors of pernicious anemia. There is no evidence to indicate that the disorder is sex linked or to permit a conclusion as to whether the trait for pernicious anemia is dominant or recessive.

Three cases of pernicious anemia in Negroes are reported by McCracken,<sup>2</sup> who gives a résumé of the literature dealing with the incidence of the disease in this race. According to him, approximately 3 per cent of all persons with pernicious anemia are Negroes. In the 3 cases reported, the diagnosis appears to be certain, but as the author states, it is unlikely that the patients were of pure Negro blood. He concludes that it is doubtful whether pernicious anemia ever occurs in a full-blooded Negro.

1. Cooley, T. B.: Hereditary Factors in the Blood Dyscrasias, *Am. J. Dis. Child.* **62**:1 (July) 1941.

2. McCracken, J. P.: Pernicious Anemia in the Negro, *J. M. A. Georgia* **30**:49, 1941.

Wintrobe<sup>3</sup> states that despite efforts to disprove Castle's hypothesis postulating the existence of an extrinsic and an intrinsic factor which form the antianemic principle present in liver, it is still generally accepted. Little is known concerning the chemical nature of the dietary or the gastric factor or the antianemic principle. The chief obstacle to the unreserved acceptance of Castle's theory is failure to produce pernicious anemia in animals. The author states that limiting the intake of the extrinsic factor does not produce the disease and that total gastrectomy except in "rare and unconvincing" instances has not been followed by the appearance of macrocytic anemia. Wintrobe attempted to produce such an anemia in newborn pigs by means of a diet deficient in the extrinsic factor, on the basis that mammalian fetal blood contains large red cells in relatively small numbers and assays of fetal liver have demonstrated little antianemic potency. In some of the animals macrocytic anemia did develop, but it was inconstant and could not be considered to be identical with pernicious anemia. Of great interest, however, were changes which occurred in the nervous system of the animals, as they simulated, in some respects, those encountered in patients with pernicious anemia. There was selective degeneration of the posterior ganglion cells, the sensory portion of the peripheral nerves, the posterior nerve roots and the posterior columns of the spinal cord. The lateral columns were not affected. These changes could be prevented by the addition of whole liver and, in some instances, of yeast, to the diet. They were not prevented by supplements of thiamine, nicotinic acid or riboflavin. Recently Wintrobe has observed that the addition of pyridoxine, choline and pantothenic acid, together with the three components of the vitamin B complex just mentioned, prevented lesions in the nervous system of the experimental animals. He regards pernicious anemia as a multiple deficiency disease and suggests that the antineuritic substance which prevents the development of the neural lesions in the pig may be the same factor which is lacking in cases of "dry" beriberi. According to him, there is increasing evidence that thiamine hydrochloride is not the antineuritic substance lacking in that deficiency disease.

Changes in the Bone Marrow: A decade ago, according to Israels,<sup>4</sup> the understanding of the anemias was facilitated by a simple diagram of red blood cell development, such as that given by Witts in his Goulstonian lectures in 1932. In this scheme the successive stages in the development of the erythrocyte were represented by (1) the reticulo-endothelial cell; (2) the megaloblast; (3) the normoblast, and (4) the

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3. Wintrobe, M. M.: Attempts to Produce Pernicious Anemia Experimentally, *Bull. New England M. Center* 3:13, 1941.

4. Israels, M. C. G.: Morbid Red Cell Development and Treatment of Anemia, *Lancet* 2:207, 1941.

erythrocyte. Failure at stage 1 caused aplastic anemia, at stage 2 pernicious anemia and at stage 3 microcytic iron-deficiency anemia. The author regards this exposition as "inadequate" in the light of present knowledge and states that there is a trend to return to more complex theories of maturation, such as those originally advanced by Naegeli and by Ferrata. Reference should be made to the original article for a statement of the view concerning the development of red cells which he states is now held by a majority of hematologists. On this basis, there are believed to be four types of pathologic erythropoiesis. According to the author, the marrow in patients with pernicious anemia is characterized by a megaloblastic hyperplasia in which are encountered all types of megaloblast, in addition to the more primitive preerythroblast and the hemocytoblast and their transition forms. After the administration of the active principle of liver, there are a prompt change to a normoblastic hyperplastic type of marrow and eventually a return to a normal marrow. Israels suggests that the liver principle is required for the maturation of normoblasts from preerythroblasts. When it is deficient, megaloblasts appear in an attempt to compensate for the absent normoblasts. A megaloblastic marrow, he believes, is the only certain indication for liver therapy. It occurs in association with addisonian pernicious anemia, with dietary deficiencies and with malabsorption from the gastrointestinal tract. All patients exhibiting such a marrow picture do not respond to liver therapy. There is, for example, a condition designated by Wilkinson as achrestic anemia, in which, in spite of a megaloblastic marrow reaction, the patients appear to be unable to utilize the liver principle.

According to Limarzi, Jones and Levinson,<sup>5</sup> many hematologists believe that megaloblasts and normoblasts follow independent lines of maturation after the earliest reticular stage has been passed, as evidenced by the marrow of patients with pernicious anemia in relapse. After the administration of liver, the marrow may be converted to the normoblastic type within forty-eight hours, and the question is raised of the mechanism of the disappearance of the megaloblasts. The authors believe that they have a clue in the finding of bizarre, multipolar mitoses and large, multinucleated, hemoglobinized cells in the marrow of patients with pernicious anemia undergoing therapy with liver extract or a preparation containing arsenic. Apparently, it is their belief that the megaloblasts disappear by means of this unusual form of erythropoiesis.

Although other investigators have studied the effects of antianemic substances on the blood of newborn rats or of the fetus in the terminal

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5. Limarzi, L. R.; Jones, R. M., and Levinson, S. A.: Unusual Erythropoiesis in the Human Sternal Marrow and Its Possible Relation to Megaloblastic Maturation, *Anat. Rec.* **79** (supp. 2):43, 1941.

stages of development, Jones<sup>6</sup> observed the changes produced in the prehepatic generation of red cells. Such cells proliferate, elaborate pigment and exhibit evidence of maturation before the liver is morphologically differentiated. He concludes that when normal pregnant rats are fed diets containing desiccated hog stomach, some antianemic substance is absorbed from the gastrointestinal tract and is transmitted through the placenta to influence prehepatic embryonic erythropoiesis. Its active presence is indicated by a reduction in the mean cell and the mean nuclear diameter of the primitive erythroblasts of embryonic blood.

**Role of the Stomach in Causation of Pernicious Anemia:** In the comprehensive review of Petri and Jensenius<sup>7</sup> all reports in the literature of the operations on the stomachs of animals on which blood studies have been made are carefully considered. From this survey it is concluded that either total gastrectomy or partial resection of the stomach in dogs, swine, monkeys or rats may result in the development of various types of anemia. Its nature appears to depend on the species of animal employed and the variety of operation performed. It should be emphasized, however, that in none of the experiments have the typical characteristics of pernicious anemia been produced, namely, hyperchromic, megalocytic anemia; hyperplasia of the bone marrow, and capacity to react characteristically to liver therapy. Nor has it been possible consistently to produce typical pernicious anemia in animals when various toxic agents and abnormal diets have been employed subsequent to the operative procedure. It is conceded that in "a few cases" there has been observed a blood picture somewhat suggestive of pernicious anemia. In gastrectomized pigs, and to a lesser extent in other experimental animals, there has appeared severe, chronic and fatal pellagra. In dogs, swine, monkeys and rats the most common type of anemia produced has been the hypochromic variety. A hyperchromic anemia has been observed after resection of the pylorus of the stomach in swine, and it is suggested that on the basis of evidence at hand, this species is suitable for further experimentation. It is the authors' belief that the failure to produce pernicious anemia experimentally in animals may be due to (1) nonexistence of this type of anemia in animals; (2) production of the intrinsic factor by the duodenum and perhaps other parts of the gastrointestinal tract, or (3) a possibility that a disturbance of some unknown factors is required in addition to gastrectomy and

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6. Jones, O. P.: Transmission of Antianemic Principle Across the Placenta and Its Influence on Embryonic Erythropoiesis: Quantitative Effect of Diets Containing Ventriculin, *Arch. Int. Med.* **68**:476 (Sept.) 1941.

7. Petri, S., and Jensenius, H.: Experimental Studies on Production of Pernicious Anemia by Operation on the Digestive Tract: Survey of the Results of Total Gastrectomy and Resections of the Stomach, *Acta med. Scandinav.* **106**: 274, 1941.

gastroduodenal resection. The possibility that Castle's theory of the causation of pernicious anemia is incorrect is also considered by the authors. They have compiled an extensive bibliography, which should be useful in further investigations of this subject.

Meyer, Schwartz and Weissman<sup>8</sup> report a case of pernicious anemia following radical resection of the stomach and state that a total of 54 cases of such an occurrence have been described in the literature. In the published accounts the following points were usually stressed: The symptoms and the typical hematologic picture develop within two to fifteen years after the operation; evidences of subacute combined degeneration of the spinal cord often accompany the anemia; gastrointestinal symptoms and, of course, achlorhydria are almost always observed, and the response to anti-pernicious-anemia therapy is specific and dramatic.

The development of hypochromic anemia following simple gastroenterostomy for peptic ulcer has been noted on many occasions, but the appearance of macrocytic anemia is a much less common occurrence. Two cases of the latter type of anemia following gastroenterostomy, reported by Gordon and Japa,<sup>9</sup> are of considerable interest. In both cases the patients were men, aged 52 and 62 respectively, and had been operated on for duodenal ulcer. In 1 instance the anemia developed eleven years and in the other twenty-eight years after the operation. In both cases severe macrocytic anemia with a high color index was observed, and in each case a satisfactory response was obtained after administration of liver extract. According to the authors, the condition may be attributed to two causes: First, there may be a lack of intrinsic factor, and, second, impaired interaction of the extrinsic and the intrinsic factor and malabsorption may be operative. A case of macrocytic anemia developing ten years after partial gastric resection for ulcer or carcinoma is reported by Hagyard.<sup>10</sup> The anemia responded well to liver therapy, but the patient eventually died of a neoplasm of the remaining portion of the stomach, believed to be a second carcinoma.

Miller<sup>11</sup> observed that achlorhydria was present in 6 of 50 infants during the first month of life, an incidence giving the same percentage as that found by Strauss and Castle in pregnant women. Additional studies were made on the gastric secretion in 63 mature and 64 premature infants in a fasting state within eight hours of birth. Twenty-

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8. Meyer, K. A.; Schwartz, S. O., and Weissman, L. H.: Pernicious Anemia Following Total Gastrectomy, *Arch. Surg.* **42**:18 (Jan.) 1941.

9. Gordon, N. S., and Japa, J.: Macrocytic Anaemia Following Gastroenterostomy, *Brit. M. J.* **2**:769, 1941.

10. Hagyard, C. E.: Pernicious Anemia and Cancer of the Stomach, *Northwest. Med.* **40**:125, 1941.

11. Miller, R. A.: Observations on Gastric Acidity During the First Month of Life, *Arch. Dis. Childhood* **16**:22, 1941.

seven of these normal infants exhibited achlorhydria. It would be of great importance to follow up these infants in order to determine whether some of them have persistent achlorhydria throughout life. It is the belief of many persons, but one difficult to prove, that patients with pernicious anemia have permanent achlorhydria on an inherited basis, present from birth. The findings of Miller are consistent with such a belief, but it is the opinion of other observers that congenital absence of gastric hydrochloric acid does not exist.

Dick<sup>12</sup> was led to investigate the bacterial content of the stomach because surprisingly little is known concerning it. The normal empty stomach has usually been considered essentially sterile; some bacteria are ingested with the food, but as acid secretion begins, the bacteria are rapidly killed. If the acidity is below normal, sarcinae, yeasts or *Oppler-Boas* bacilli may multiply. Studies were made by Dick on stomach contents obtained just before stimulation with histamine and again about three quarters of an hour afterward. He found that almost all specimens containing free hydrochloric acid were sterile. In patients with pernicious anemia it was observed that the numbers of bacteria were constantly and surprisingly large, that all blood agar plates showed a predominance of green-forming streptococci, that in all instances organisms of the colon group grew on the litmus lactose plates and that of the eighteen anaerobic cultures, eleven showed long gram-negative threadlike filaments, forming dense tangled masses in the slides. Dick asks whether the enormous number of bacteria encountered in patients with chronic gastritis, with or without pernicious anemia, are present as a result of the loss of the normal bactericidal power of the gastric juice or whether they are the agents causing the disease. In his opinion the former explanation is inadequate, and furthermore, he finds it difficult to explain the almost constant presence of bacteria of the colon and the lactic-aerogenes group on the basis of ingestion and subsequent growth due to achylia. He is inclined to believe that there is a profound derangement of the whole gastrointestinal tract in patients with pernicious anemia and with some other types of chronic gastritis, permitting the return of colon bacilli from the colon to the stomach. He finds that the litmus lactose plates cultured with the stomach contents of patients with pernicious anemia cannot be distinguished from litmus lactose plates obtained with normal stools.

A scholarly discussion by Rhoads<sup>13</sup> bears on the possible relations between gastritis, pernicious anemia and cancer of the stomach. He makes the cogent suggestions that certain forms of gastritis are in fact

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12. Dick, G. F.: Bacteriologic Examination of Stomach Contents in Pernicious Anemia, *Am. J. Digest. Dis.* 8:255, 1941.

13. Rhoads, C. P.: Gastric Cancer as a Sequel to Gastritis, Particularly the Gastritis of Pernicious Anemia, *J. Nat. Cancer Inst.* 1:511, 1941.

precancerous alterations, they are the result of a food deficiency and they may be cured by adequate dietary means. He does not intend to imply, however, that all gastric cancers or any large number of them are the result of dietary deficiencies, nor is it his belief that the malignant change, once established, can be reversed by dietary means. His tentative suggestions are based on the following observations: 1. Gastritis accompanies and probably precedes the development of gastric cancer in certain cases. 2. The association of pernicious anemia and its ever present gastritis with gastric cancer is more frequent than can be explained by the laws of chance. 3. There is some evidence that if one of the disorders is present in a family, the other is likely to occur. 4. Gastric cancer as a sequel of pernicious anemia is not infrequent, and gastric polyposis is much more commonly encountered at necropsy in patients with pernicious anemia than in those with other disorders. 5. Gastroscopic observations indicate that the gastritis of pernicious anemia is reversible by dietary means. It is suggested that possibly the elimination of gastritis might be a preventive measure in the control of cancer of the stomach.

Experimental Production of Pernicious Anemia: Isaacs<sup>14</sup> observed that after the subcutaneous injection of glycocholic acid from ox bile, mild macrocytic, oval red cell anemia developed in 3 of 12 rats during the course of two months. Also during this interval 1 animal was noted to have dragging of the hindlegs, with clumsy gait, and in three months 2 rats showed cutaneous ulcerations in regions which had not been used for injections. According to the author, these results suggest the hypothesis that an increase or defect in the metabolism of bile acids in persons with pernicious anemia causes an alteration in the secretion of the "intrinsic factor," resulting in the development of macrocytic anemia and permitting an increase in hemolysis. The bile acids, acting on the central nervous system, would cause the degenerative changes. Leukocytopenia would be another result. This investigator also states that he has confirmed the observations reported by Blankenhorn in 1917, that the bile acids are increased in the blood of patients with pernicious anemia in relapse.

Crandall, Finne and Smith<sup>15</sup> report the production of macrocytic anemia in dogs by the creation of an internal bile fistula (anastomosis of the gallbladder to the right renal pelvis with ligation of the common bile duct). They attribute the anemia to a deficiency in the anti-pernicious-anemia factor resulting from impaired intestinal absorption. They mention, however, the possibility of hepatic dysfunction due to

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14. Isaacs, R.: Production of Pernicious Anemia-Like Syndrome in Rats with Bile Acids, *Proc. Soc. Exper. Biol. & Med.* **45**:794, 1940.

15. Crandall, L. A., Jr.; Finne, C. O., Jr., and Smith, P. W.: Experimental Anti-Pernicious Anemia Factor Deficiency in Dogs, *Science* **93**:549, 1941.

failure of the recirculation of bile, thereby producing macrocytic anemia comparable to that occurring in patients with hepatic disease.

Smith, Reiser and Harrell<sup>16</sup> fed young swine a diet which was partially deficient in the vitamin B complex for a long period and observed severe macrocytic anemia. Similar anemias associated with a deficiency of factors of the vitamin B complex have previously been reported from different laboratories. The unique observation made in this study, however, was the spontaneous recovery from the anemia while the animals remained on the same diet and were without treatment of any kind. The authors offer the explanation that the diet may have been inadequate during the period preceding sexual maturity, but that after sexual stability had become established all of the nutritional requirements of the animal were met.

Relation of *Diphyllbothrium* Infection to Macrocytic Anemia: It had been noted previously by von Bonsdorff<sup>17</sup> that aqueous extracts of certain intestinal worms, including *D. latum*, had a considerable inhibitory effect on the proteolytic activity of normal human gastric juice in vitro at approximately the neutral point. This was not true of the activity of other proteolytic enzymes, such as trypsin, pepsin and papain. In the present investigation, this phenomenon has been subjected to a more intensive study. It was found that relatively small amounts of a suspension of fresh *D. latum* have a pronounced inhibitory effect on the gastric protease which is active at a  $p_H$  range from 5 to 9 and above. According to the author, this enzyme is supposedly identical with the "intrinsic factor." The inhibitory effect on the proteolytic activity depends on the  $p_H$  at which the aqueous extracts are prepared (proved for  $p_H$  1.7 to 9.0). It is not conditioned by any product arising during the autolysis of the worm; in other words, the inhibitory substance is to be found preformed in the worm.

In a second article von Bonsdorff<sup>18</sup> reports observations on the etiologic relation between *D. latum* and the associated macrocytic anemia. He mentions that in recent years there has been a tendency, especially in America, to regard the presence of this intestinal parasite and the anemia as nothing more than a coincidence. The author emphasizes the following important observation: The condition produced by this

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16. Smith, S. G.; Reiser, R., and Harrell, G. T.: Spontaneous Recovery from Nutritional Macrocytic Anemia in Young Swine Following Initial Estrus, *J. Clin. Investigation* **20**:369, 1941.

17. von Bonsdorff, B.: Inhibitory Effect of *Diphyllbothrium Latum* on Proteolytic Activity in Vitro of Depepsinized Human Gastric Juice. *Diphyllbothrium Latum* and Pernicious Anemia, *Acta med. Scandinav.* **105**:502, 1940.

18. von Bonsdorff, B.: On the Reticulocyte Response and Course of Remission After Removal of the Worm in Patients with *Diphyllbothrium Latum* and Pernicious Anemia; *Diphyllbothrium Latum* and Pernicious Anemia, *Acta med. Scandinav.* **105**:516, 1940.



intestinal parasite agrees in all essentials with true addisonian anemia in regard to clinical manifestations, hematologic changes and alterations in the bone marrow; tapeworm anemia can be controlled with liver and stomach preparations; the condition can be cured by the expulsion of the worm, which indicates that the parasite in some manner interferes with the endogenous production of the anti-anemic principle (the pernicious anemia factor). In general, this author has observed the following relations between the intestinal parasite and the host, so far as they affect the production of macrocytic anemia: When the expulsion of the parasite is followed by a definite reticulocyte response and active red cell regeneration, it is considered conclusive proof of the causal relation between the anemia and the intestinal infection. When the expulsion of the worm is not followed by a remission, the association is apparently only incidental. In still other instances, it appears that the infection intensifies the course of true cryptogenic pernicious anemia.

The purpose of the third communication by von Bonsdorff<sup>19</sup> is to bring information to bear on the understanding of the pathogenesis of "pernicious tapeworm anemia." Since the author believes that the proteolytic gastric enzyme active at a neutral reaction may be "identical with Castle's intrinsic factor," a possible means is thus afforded to determine the presence of the intrinsic factor in cases of "pernicious tapeworm anemia." It was concluded from observations on patients that the gastric juice contains the proteolytic enzyme active at neutral reaction both when the pernicious anemia is caused by the infection with the worm and when the causal relation is uncertain for various reasons. To us the importance of these studies is almost wholly dependent on the substantialness of the proof that the protease and the intrinsic factor are identical.

Studies on the Active Principle of Liver: In the fourteen years which have elapsed since the original announcement of Minot and Murphy that liver is effective in the treatment of pernicious anemia, several groups of investigators have endeavored unsuccessfully to isolate chemically the hematopoietically active material present in liver. Advances in this direction have been made, however, and these are summarized by Jacobson and Subbarow.<sup>20</sup> According to these authors, the greatest difficulties which have hampered this investigation have been, first, the lack of a method of assay in animals and, second, the apparent loss of therapeutic activity which develops as the fractionation

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19. von Bonsdorff, B.: On the Proteolytic Activity in Vitro at Neutral Reaction of Gastric Juice from Patients with Cryptogenetic Pernicious Anemia and with Pernicious Anemia Due to *Diphyllobothrium Latum*; *Diphyllobothrium Latum* and Pernicious Anemia, *Acta med. Scandinav.* **105**:540, 1940.

20. Jacobson, B. M., and Subbarow, Y.: Studies of the Principle in Liver Effective in Pernicious Anemia: Recent Advances in the Purification of Active Substances, *J. A. M. A.* **116**:367 (Feb. 1) 1941.

proceeds, even in the absence of destructive chemical and physical procedures. The original groundwork of the problem was laid by Cohn and his collaborators between 1927 and 1930. Their technic involved the removal of the bulk of liver proteins and leaving as a residuum a therapeutically active yellow powder. This they designated as "Fraction G." Additional steps of purification yielded an amorphous material which had more of the characteristics of a nitrogenous base and was effective in the treatment of pernicious anemia. Since this work, additional studies by others have shown that the therapeutically active material may be precipitated by Reinecke's (tetrathiocyanodiamino-chromic) acid and by saturated ammonium sulfate. Furthermore, several investigators discovered independently that the active material was adsorbed quantitatively by charcoal, from which it could be eluted by alcohol or phenol. These studies have fallen short of the final goal, as they have not resulted in isolation from liver, in a pure chemical form, of a principle that completely duplicates the therapeutic activity of that organ. It was first suggested by Fiske, Subbarow and Jacobson in 1935 that the anti-pernicious-anemia effect of liver is due, not to a single chemical compound, but to the combined action of several substances. As direct evidence in support of their theory, Jacobson and Subbarow cite the observation that with the continued purification of crude liver extract, in the absence of destructive procedures, there is a complete or partial loss of potency. However, the administration of the purified materials with other liver fractions, which they term accessory factors, results in the recovery of the lost therapeutic activity. These accessory factors are by themselves therapeutically inert. It is the authors' present belief that there are at least five such factors, including l-tryosine, a complex purine, a peptide, tryptophan and guanosine. The authors summarize the recent reports of others concerning the more highly purified therapeutically active liver substances and emphasize that both concordant and discordant properties are ascribed to them. It has been suggested by one group of investigators that the active principle is an  $\omega$ -amino or imino acid and that it is definitely not a purine or a pyrimidine base. The possibility has not been excluded, however, that it may be a ring compound of the pyrrole or pyridine type. Studies by others suggest that the active material is, or is associated with, a peptide. The authors conclude that "until the primary factor is obtained in crystalline form, this discordant state" of knowledge will exist. That all workers in this field are not in accord with the conclusions of Jacobson and Subbarow is indicated by the discussion of their presentation by West, who emphasizes that the mixture of peptides described by Dakin and others does not contain any of the accessory factors mentioned.

Aylward and his associates<sup>21</sup> carried out an interesting study to determine the anti-pernicious-anemia activity of various mammalian livers. In order to test for the active principle, an extract was prepared with the usual technic and injected intramuscularly into patients with pernicious anemia in relapse. The livers of many species of herbivorous and carnivorous mammals were utilized. All of the extracts with the exception of that made from sea lion liver were shown to possess therapeutic activity. This indicates that the anti-pernicious-anemia principle is stored in the livers of a large variety of mammals, despite the fact that the disease does not occur spontaneously in animals and cannot be produced experimentally. The authors conclude, therefore, that knowledge of the biochemical and physiologic processes involved in normal hemopoiesis and of the deficiencies leading to the various anemias is far from complete. Reference is made to previous studies which have shown that stomach preparations derived from human beings, pigs and silver foxes are active. Stomachs obtained from herbivorous animals are said to have little or no hemopoietic activity.

**Relation Between Pernicious Anemia and Other Diseases:** A discussion of the possible relation between "primary" hypochromic anemia and pernicious anemia is given by Miller and Dameshek,<sup>22</sup> and 2 cases are recorded in which the hypochromic type of anemia terminated in the pernicious variety. According to them, this association is of interest for the following reasons: 1. In both conditions achlorhydria is almost invariably present. 2. Total gastrectomy or widespread neoplastic involvement of the stomach may be followed by either type of anemia. 3. It is occasionally reported that 1 or more members of a family had pernicious anemia, while others showed hypochromic anemia. 4. There have been occasional previous reports of hypochromic anemia which terminated in the pernicious type. In 1 of the authors' cases, the Plummer-Vinson syndrome was present and the response to iron was good. This response was followed several years later by recurrence of anemia and subsequent improvement induced by liver extract therapy. In the second case of hypochromic anemia the evidence of pernicious anemia developed after the administration of iron. In this case it was considered that both an iron and a liver extract deficiency were present and that response to medicinal iron "unmasked" the underlying macrocytic anemia. A review of the literature and a discussion of the possible mechanisms and theoretic implications are included.

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21. Aylward, F. X.; Grieve, W. S. M.; Mainwaring, B. R. S., and Wilkinson, J. F.: Hemopoietic Activity of Mammalian Livers, *J. Physiol.* **100**:94, 1941.

22. Miller, E. B., and Dameshek, W.: "Primary" Hypochromic Anemia Terminating in Pernicious Anemia: Report of Two Cases, *Arch. Int. Med.* **68**: 375 (Sept.) 1941.

Stenstam<sup>23</sup> gives a digest of previous publications dealing with the relation between pernicious anemia and exophthalmic goiter and adds a number of cases in which he has observed this association. In his opinion, the combination is rare but not as infrequent as some authors have stated. Approximately 50 cases, in which the patients were preponderantly women, have been reported in the literature. Usually the symptoms of exophthalmic goiter preceded those of anemia, and in a majority of instances the latter have appeared at an earlier age than is usual in pernicious anemia. According to Meulengracht's theory, in cases of such a combination the pernicious anemia may develop on the basis of the achlorhydria which is known to occur frequently in patients with thyrotoxicosis. The mechanism included may be stated as follows: Persons with a disposition toward pernicious anemia inherit a vulnerable and sensitive digestive tract mucosa, which after a period of years is unable to produce a normal amount of "intrinsic factor." It is assumed that a mucous membrane of this sort will be damaged more rapidly in a patient with thyrotoxicosis. Means expresses the situation excellently in these words: "Thyrotoxicosis brings out the individual's weak points." As a result, evidences of pernicious anemia appear at an earlier age than is usual. The author concludes, however, that the combination of these two diseases may also be fortuitous. The total number of patients admitted to the Medical Clinic at Lund, Sweden, for a ten year period numbered 28,414, among which were 389 with exophthalmic goiter and 193 with pernicious anemia. In only 3 instances did the two diseases coincide in the same patient. The author believes, however, that improved diagnostic resources and, above all, a sharper look-out for the occurrence of such a combination, will increase the number of instances detected and reveal that the combination is not exceedingly rare.

Other Observations Relating to the Etiology of Pernicious Anemia: In 1935 Wakerlin recorded the observation that the urine of patients with untreated pernicious anemia contained a reticulocyte-decreasing factor for the pigeon which was not present in the urine of 6 normal persons and 2 treated patients with pernicious anemia. Since this report additional studies<sup>24</sup> have led the author to conclude that the toxic reticulocytopenic factor occurs inconstantly in the urine of untreated patients with pernicious anemia and that it is not specific for pernicious anemia but is present also in the urine of patients with other diseases (diffuse carcinomatosis, subacute bacterial endocarditis and aplastic anemia). The evidence suggests that the factor is incidental and resultant and not pathogenic in its relation to pernicious anemia.

23. Stenstam, T.: Pernicious Anemia and Basedow's Disease, *Acta med. Scandinav.* **104**:29, 1940.

24. Wakerlin, G. E.: The Toxic Factor in Pernicious Anemia, *Am. J. Physiol.* **133**:478, 1941.

An anonymous writer<sup>25</sup> emphasizes the importance of the vitamin B<sub>2</sub> complex, which is defined as an assemblage of some of the water-soluble vitamins present in yeast. The author cites the work of Manson-Bahr, who claimed that glossitis, probably nonspecific, is encountered in pellagra, sprue, pernicious anemia, the nutritional anemias and idiopathic steatorrhea. Because of this and other features, including changes in the spinal cord, such diseases are considered to be closely related to each other. The commentator believes that nicotinic acid and riboflavin play an important role in the treatment of sprue as well as of pellagra, pernicious anemia, subacute combined degeneration of the spinal cord and, to some extent, idiopathic steatorrhea. The reviewers are willing to concede this possible relation, but it is difficult to prove the precise nature of such an association. It should be considered a fruitful field for further investigation.

A detailed discussion of the etiology of the anemias, including pernicious anemia, is presented by Sturgis.<sup>26</sup>

*Treatment of Pernicious Anemia.*—A majority of students of the disease will agree with Askey's<sup>27</sup> statement that the treatment of pernicious anemia is true substitution therapy which does nothing to remove directly the cause of the primary deficiency of Castle's intrinsic factor. He contends that optimum therapeutic results can be attained by the administration of a massive dose of liver extract, calculated to contain theoretically the amount of the active principle which is lacking in the liver plus the quantity needed immediately by the body for tissue repair. This is estimated to be between 100 and 300 U. S. P. hemopoietic units. Whether such huge doses are stored or partially excreted is difficult to prove. It is feasible, however, to gain some idea of storage of the active principle in liver indirectly by observation of the changes in the peripheral blood. In an attempt to throw light on this point, Askey during a three year period gave massive doses of liver extract to 22 patients who had pernicious anemia in relapse. An initial dose of 15 or 20 U. S. P. units was given intramuscularly. On the following day a massive dose of 150 to 400 U. S. P. units was injected into the buttocks. No further anti-pernicious-anemia therapy was given during a subsequent period of observation. In only 3 of 19 patients was the red cell count below 4,000,000 at the end of two months. In the other 16 patients the average red cell count at the end of one month was 4,050,000, at two months 4,750,000 and three months 4,700,000 per

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25. Glossitis and the Vitamin B<sub>2</sub> Complex, Current Comment, M. J. Australia **1**:304, 1941.

26. Sturgis, C. C.: Etiology of the Anemias, Am. J. Pub. Health **31**:10, 1941.

27. Askey, J. M.: Quantitative Treatment of Pernicious Anemia: Response to Initial Massive Dose of Liver Extract in Relapse, J. A. M. A. **117**:907 (Sept. 13) 1941.

cubic millimeter. The clinical responses of these 16 patients were excellent. The following criteria were considered as evidence of relapse: a red cell count of less than 4,000,000; any increase in paresthesia, or a definite loss of strength. Of the 16 patients, 1 relapsed at three months, 3 at four months, 2 at five months, 2 at six months and 1 at ten months after the initial treatment. In comparison with the studies of Strauss in 1940, these data are interpreted by the author as suggesting that a greater liver storage is effected by a single large dose than by repeated small doses. He has shown conclusively that the majority of patients in relapse can be given a single massive dose which will establish and maintain for several months a normal red cell count with satisfactory clinical improvement. According to Askey, after the initial large dose it is advisable to keep the liver in a state of optimum storage, which, in his opinion, can best be accomplished by the monthly injection of "suitable amounts."

Seymour, Heinle and Miller<sup>28</sup> have recently reported interesting studies on the storage of the hemopoietic principle by patients with pernicious anemia. Nine patients with therapeutically induced remission were given parenterally 55 to 140 U. S. P. units of liver extract over a period of ten to thirty days. Subsequently, further anti-pernicious-anemia therapy was withheld until the blood showed evidence of relapse. These remissions continued for sixteen to forty-four weeks and were, in general, shorter than when the identical amount of liver extract was given in small, intermittent doses. Crude and concentrated preparations of liver extract appeared to be equally effective so far as maintenance of blood levels was concerned. Thirteen patients in relapse were given 90 to 380 U. S. P. units of liver extract intramuscularly during periods of ten to thirty days. In all of these patients, remissions were induced and blood levels were maintained for thirteen to twenty-nine weeks without further treatment of any sort. It was concluded that if the hemopoietic principle is stored in the body, such storage is not quantitative when large doses of liver extract are administered over a short interval. It is the authors' opinion that the fate of the unused hemopoietic principle is unknown. Furthermore, it is considered that the degree of deficiency of the intrinsic factor and the amount of the extrinsic factor in the diet of patients with pernicious anemia probably account for individual variations in requirements of liver extract. They also observed that by augmenting the extrinsic factor in the diet, 2 patients with mild pernicious anemia were maintained in remission for long periods without any additional specific treatment.

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28. Seymour, W. B.; Heinle, R. W., and Miller, F. R.: Liver Dosage in Pernicious Anemia: Failure of Quantitative Storage of Hematopoietic Principle, *New England J. Med.* **225**:675, 1941.

Evans and Jordan<sup>29</sup> support the belief, generally accepted, that the most effective method of treating patients with pernicious anemia is intramuscular injection of liver extract. Their statements are based on the observations of 40 patients treated with a preparation containing a mixture of liver extract and thiamine hydrochloride. The average dose was 1 cc. (20 U. S. P. units) of liver extract administered intramuscularly every three or four weeks, and the patients were followed up in most instances for two to four years. The authors' conclusions are based on the dose necessary for the maintenance of a patient with pernicious anemia in a state of well-being and good health. They observed that with the dose used, the red cell count and the hemoglobin level were maintained at satisfactory figures, the symptoms and signs referable to the nervous system were controlled or actually improved in a great majority of cases and the patients were able to combat many types of acute and chronic disease almost as effectively as members of the general population. Finally, they emphasized that the cost of this type of treatment is not prohibitive. They are not in accord with the belief that the less refined extracts of liver contain a substance, absent in the more concentrated types, which has a beneficial effect on the lesions of the nervous system.

Bethell<sup>30</sup> regards pernicious anemia as a multiple deficiency disease, not caused primarily by lack of food factors, but by defective modification, absorption and utilization of dietary substances. As regards specific therapy, the intramuscular injection of liver extract is given as the method of choice, and the recommended initial dose for most patients in relapse is 15 U. S. P. units daily for one week. Subsequently, a similar amount is given three times weekly until the blood reaches normal limits. The maintenance dose varies considerably, but in general a reliable amount is 15 units every one or two weeks. In a few instances, the treatments can be given at longer intervals. If a more dilute extract is used, the daily dose in relapse should be 4 to 6 cc. (of which 1 cc. is obtained from 5 Gm. of whole liver). An equal amount given at intervals of one to two weeks has been found to be satisfactory for a maintenance dose. Oral therapy has a place in the management of patients who object to the parenteral route and whose blood values can be maintained with reasonable amounts of material. Furthermore, oral stomach therapy is indicated in the 2 per cent of patients with pernicious anemia who become sensitized to liver, although under such circumstances desensitization to liver may be attempted. Ninety per cent of the patients in the group

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29. Evans, T. S., and Jordan, R. H.: Concentrated Liver Extract in the Maintenance Treatment of Pernicious Anemia, *Am. J. M. Sc.* **202**:408, 1941.

30. Bethell, F. H.: The Treatment of Pernicious Anemia, *J. Omaha Mid-West Clin. Soc.* **2**:23, 1941.

observed by Bethell had symptoms referable to the nervous system. In general, it could be said that improvement of such symptoms occurred in proportion to the completeness of the hematologic remission and the highest incidence of good therapeutic results was observed among patients treated by the intramuscular injection of a concentrated liver extract. Of these patients, 84.6 per cent showed improvement, in 13.5 per cent the condition remained unchanged and in only 1 patient did the manifestations in the nervous system become more prominent. Beneficial results occurred as frequently and to as great a degree in those receiving refined extracts as in those to whom cruder preparations were given. Vitamin B in the form of powdered yeast was considered to be of some value in the treatment of the lesions of the nervous system, although the effectiveness of this substance is difficult to evaluate. It is insisted by Bethell that adequate maintenance therapy should not be governed by the clinical state of the patient. In his opinion safer and more reliable criteria are afforded by the condition of the blood, indicated in order of relative value by the mean corpuscular volume, the color index and the red cell count.

Haden<sup>31</sup> gives definite recommendations concerning the treatment of the macrocytic and the iron deficiency anemias by means of anti-pernicious-anemia therapeutic agents and by iron. Reference will be made here only to the treatment of pernicious anemia. He recommends the parenteral use of liver extract as the treatment of choice, for it is less expensive and more effective. When the patient first presents himself with pernicious anemia in relapse, a subcutaneous injection of 1 cc. of a concentrated liver extract containing at least 15 U. S. P. units of the active principle is given daily for fourteen days. During this time if possible the patient is kept in bed. With the return of the appetite, usually on the fifth to the seventh day, the anemia diet with the addition of a liver cocktail is begun. The latter is made from equal parts of ground broiled liver and tomato juice with the addition of a teaspoonful of yeast extract (vegex). After the initial period of intensive therapy, injections of liver extract are given twice a week for three months. For the second three months an injection is given once a week, and for the following six months, once every two weeks. After the lapse of one year one injection each month is usually all that is required if a preparation containing 15 units per cubic centimeter is used. However, unless accurate blood studies are regularly done, we recommend as a safer procedure for most patients the injection of 15 units every one or two weeks. In the treatment of subacute combined degeneration of the spinal cord Haden recommends that a less concentrated preparation (5 units per cubic

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31. Haden, R. L.: *The Specific Treatment of Anemia with Liver and Iron*, Illinois M. J. **79**:44, 1941.



centimeter) be used at more frequent intervals, as he considers that it is more effective in the treatment of the neurologic manifestations. All observers are not in accord with this statement. It is emphasized that the best criterion of efficient and complete therapy is the maintenance of the red cell volume as determined by the hematocrit readings and the red cell counts. In almost all instances, however, the erythrocyte volume is normal if the count is 5,000,000 per cubic millimeter for males and 4,500,000 for females. A complete blood study should be done at least every three months as long as the patient lives. Any increase in the red cell volume beyond the normal heralds a relapse or indicates inadequate therapy.

Bethea<sup>32</sup> gives sound and practical advice concerning the indications for the use of iron and liver in the treatment of the various anemias. Reference will be made here only to his discussion of the indications for the use of liver. Concentrated liver extract is the preparation of choice in his opinion. Indications for its use are, (1) pernicious anemia, (2) combined system disease, (3) sprue, (4) pellagra, (5) certain types of hepatic disease (cirrhosis, etc.) in which there is interference with the storage of the erythrocyte-maturing factor, (6) the macrocytic anemia of pregnancy and (7) other less frequent causes of macrocytic anemia, such as "short-circuiting" operations on the gastrointestinal tract, various types of diarrhea, carcinoma of the stomach and fish tapeworm infection. He considers that liver extract has been used with "perhaps questionable success" in the treatment of such diseases as aplastic anemia, thrombopenic purpura and agranulocytosis. He remarks, however, that the treatment of these conditions is so unsatisfactory that there is justification for giving liver extract a trial, as various observers have reported contradictory results. We are in only partial accord with this statement, as we believe that there are therapeutic methods available for the treatment of thrombopenic purpura and agranulocytosis which are more satisfactory than the parenteral administration of liver extract.

In a general article Leavell<sup>33</sup> presents a modification of Wintrobe's classification of the anemias and discusses the treatment of the various types, including pernicious anemia.

According to Sjögren,<sup>34</sup> 10 Gm. of his antianemic material designated as "hepaforte" is equivalent in action to 250 Gm. of liver. The details of manufacture are not given, but in general the product is the result of the

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32. Bethea, J. M.: Uses and Misuses of Iron and Liver Extracts in the Treatment of Anemia, *Memphis M. J.* **16**:187, 1941.

33. Leavell, B. S.: Anemia: Classification and Treatment, *Virginia M. Monthly* **68**:515, 1941.

34. Sjögren, B.: A New Stomach-Liver Preparation for the Treatment of Pernicious Anemia: The Nature of Hepaforte, *Acta med. Scandinav.* **106**:479 1941.

interaction of materials present in raw liver and stomach. He states that the most generally accepted belief is that in the normal human being the active material arises as a result of the "fermentative" action of the intrinsic factor on the substrate, which is the extrinsic factor. This is, however, not the only interpretation which may be placed on the observed facts. One could, the author argues, consider that the intrinsic factor is essential and that it undergoes "activation" by the extrinsic factor. Furthermore, it cannot be definitely established that it is necessary for a reaction to occur between the two factors, as perhaps the same result may be produced by the simultaneous action of both factors in optimum concentration. In the meantime, the exact mechanism of the action must remain an open question. The main established fact is that the two factors are interdependent and by some type of interaction can produce a product which the author claims is more potent than either stomach or liver. Bjure and Weijdegard<sup>35</sup> have reported on the therapeutic activity of hepaforte in 30 cases of pernicious anemia. They conclude that it is at least equivalent in effectiveness to other oral preparations. Ordinarily it is taken without difficulty by the patient, but occasionally, after long periods, it must be discontinued for a few days on account of nausea and vomiting. Even though it cannot be said to produce as uniformly satisfactory results as the parenteral injection of liver extract, it may be equally effective, and in some cases the authors thought that it produced even better effects, at least temporarily.

The treatment of nutritional tropical anemia, according to Trowell,<sup>36</sup> is not as satisfactory as that of the closely allied condition of true pernicious anemia. This is because few patients with the former disorder can tolerate the necessary 15 to 60 Gm. daily of autolyzed yeast (marmite), and furthermore, the therapy is expensive. Moreover, while  $\frac{1}{2}$  pound (225 Gm.) of whole liver daily is an adequate amount for the treatment of a patient with pernicious anemia, it requires about four times this much to control tropical anemia. The more concentrated liver extracts, in the opinion of the author, appear to lose in the refining process some of the fractions essential for the cure of this type of macrocytic anemia. In an attempt to find a more satisfactory form of therapy, Trowell treated 2 patients with the disease with a crude preparation of liver extract and concluded that the material was more effective, as well as cheaper, than the refined products.

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35. Bjure, A., and Weijdegard, H.: A New Stomach-Liver Preparation for the Treatment of Pernicious Anemia: Treatment of Pernicious Anemia with Hepaforte; Results Obtained in Thirty Cases, with a Description of Six Cases, *Acta med. Scandinav.* **106**:483, 1941.

36. Trowell, H. C.: Liver Extract in Treatment of Tropical Macrocytic Anaemia, *Lancet* **2**:303, 1941.

An unusual spontaneous increase in the percentage of reticulocytes to 33.4, persisting for at least two days, was noted by Cooke<sup>37</sup> in a patient with pernicious anemia. Inquiry into her dietetic habits disclosed that she did not consume excessive amounts of meat, that she was accustomed to have liver once weekly and that she had had no liver therapy from her physician. The patient had glossitis and achlorhydria and gave a characteristic response to injections of liver extract. Comment is made that little information is available concerning the number of reticulocytes which are present in spontaneous remissions in patients with pernicious anemia, although what data are available seem to indicate that the percentage of reticulocytes usually does not rise above 8 to 10.

According to the views of Buding,<sup>38</sup> failure to respond to anti-pernicious-anemia therapy with potent agents may be due to a lack of vitamins in the diet. In support of this belief he cites 2 patients with the disorder who did not give the anticipated response to large doses of potent liver extract. One had gastrointestinal disturbances and existed largely on a diet of gruels and other foods which were not good sources of nicotinic acid or its amides. The other had a food intake consisting chiefly of carbohydrates, which in themselves increase the demand for vitamin B<sub>1</sub>. The needs for this vitamin were further augmented because the patient had exophthalmic goiter. Moreover, the presence of achlorhydria may cause malabsorption of various essential food products. The first patient did not show the proper response in the blood until nicotinic acid amide was administered in addition to the liver extract, and the second patient improved strikingly when vitamin B<sub>1</sub> was added to the diet.

It is believed by Beiglböck<sup>39</sup> that the vitamin B complex plays some role in the causation of pernicious anemia. In support of this he reports his observations on the therapeutic effect of yeast preparations on 4 patients with the disease. Three patients gave a response to this material alone, and in the other an effect was obtained when yeast was supplemented by gastric juice. The author emphasizes that the glossitis, the clinical evidences of subacute combined degeneration of the spinal cord and the polyneuritis were more favorably influenced by yeast than by liver extract.

The London correspondent of *The Journal of the American Medical Association* makes some interesting observations concerning the availa-

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37. Cooke, W. T.: Unusual Reticulocytosis in an Untreated Case of Pernicious Anaemia, *Brit. M. J.* **2**:806, 1941.

38. Buding, A.: Ein Beitrag zur Therapie der leberrefraktären perniziösen Anämie, *Deutsche med. Wchnschr.* **67**:591, 1941.

39. Beiglböck, W.: Vitamin B und perniziöse Anämie, *Wien. klin. Wchnschr.* **54**:327, 1941.

bility of liver in England and the treatment of pernicious anemia.<sup>40</sup> On account of the present shortage of liver the Food Rationing Committee of the Medical Research Council was asked by the Ministry of Food to advise them concerning the requirements of fresh liver for the treatment of pernicious anemia. Their recommendation was that fresh liver is unnecessary except in those rare cases in which the parenteral injection of liver extract produces anaphylactic shock. They consider that treatment by parenteral injection is more efficient than treatment by the ingestion of raw or lightly cooked liver, and it is the cheapest method of therapy. It is emphasized that treatment cannot be considered as satisfactory unless the red cell count is maintained at 5,000,000 per cubic millimeter and the hemoglobin concentration at 100 per cent. With lower values, the patient may not have any complaints, but there is danger of development of subacute combined degeneration of the spinal cord. The amount of fresh liver necessary to maintain these values is such that few patients will take it indefinitely. On the other hand, the intramuscular injection of 1 to 2 cc. of liver extract at intervals of seldom less than one to two weeks is sufficient for maintenance of normal blood levels. The Committee does not advise the oral use of liquid or powdered preparations of liver, for these, though efficacious, are uneconomical, as about fifty times as much liver is required as that needed when treatment is by the parenteral route. This objection does not apply to preparations made from stomach for oral administration.

Witts<sup>41</sup> draws attention to an interesting possibility when he reminds physicians that Rhoads and Miller in 1937 demonstrated that aminopyrine will depress red cell production in animals on a defective diet. Their work suggested that care should be used in prescribing this drug to patients with pernicious anemia. As an example of the harm which might follow its use, he cites the case of a 32 year old married woman physician with pernicious anemia who experienced a drop in hemoglobin concentration from 70 to 58 per cent despite weekly injections of liver extract. Several doses of the preparation were then given on alternate days, but the hemoglobin concentration continued to fall to 46 per cent. No evidence could be found of any important complication to explain this fall in hemoglobin, but it was discovered that she had been taking a hypnotic drug containing aminopyrine. When the drug was discontinued, although no other changes in treatment were made, reticulocytosis (31 per cent) and rapid improvement occurred. Within two months her hemoglobin concentration had increased to 92 per cent.

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40. Fresh Liver for Pernicious Anemia, *Foreign Letters* (London), J. A. M. A. **117**:548 (Aug. 16) 1941.

41. Witts, L. J.: Amidopyrine and Pernicious Anaemia, *Brit. M. J.* **2**:199, 1941.

*Changes in the Nervous System in Pernicious Anemia.*—It is stated by Hemphill and Stengel <sup>42</sup> that present knowledge is as yet incomplete of those diseases of the nervous system in which the myelin sheaths and the axis-cylinders are unsystematically affected, but in which the other elements of the nervous system are spared. The group of disorders in which these changes are associated with anemia is the most clearly defined. In case of such diseases, however, typical changes of subacute combined degeneration of the spinal cord may occur which are not accompanied by gross pathologic changes in the blood. An instance is presented of the typical picture of subacute combined degeneration without changes in the blood and another in which there was extensive involvement of the brain and the peripheral nerves. Although nothing can be said regarding the origin of the condition, the pathologic findings suggest the presence of a deficiency disease with a special tendency to produce demyelination and vascular changes of the brain and the leptomeninges.

Verbrugghen <sup>43</sup> reviews the more common diseases of the spinal cord and includes subacute combined degeneration, which he states is usually associated with pernicious anemia but is rarely observed in association with long-continued cachexia or with sprue. It is emphasized that there is no constant parallelism between the extent of the manifestations in the nervous system and the alterations in the blood. He considers that the underlying cause of subacute combined degeneration is "probably" associated both with a disturbance of vitamin B metabolism and with an intrinsic gastric factor. Consequently, he believes that it is related to certain deficiency diseases, such as pellagra and lathyrism. He states that the disorder must be differentiated from multiple sclerosis, polyneuritis, spinal cord compression, tabes dorsalis and Landry's ascending paralysis. The oral administration of liver with the addition of vitamins A and B renders the outlook better than it has previously been considered, but "it cannot be stated that it is possible to arrest the disease completely." We are not in entire accord with this statement and believe that intensive treatment with liver extract may improve or at least arrest the manifestations in the nervous system in the great majority of cases.

Turner <sup>44</sup> reports 3 cases of optic atrophy in patients with pernicious anemia. In 2 instances it was the earliest symptom of the disease, and in 1 case it was preceded by fatigue for six months. There was no par-

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42. Hemphill, R. E., and Stengel, E.: Subacute Combined Degeneration of Unknown Origin with Extensive Involvement of the Brain, *J. Ment. Sc.* **87**:77, 1941.

43. Verbrugghen, A.: The More Common Nervous Diseases of the Spinal Cord, *J. Iowa M. Soc.* **31**:415, 1941.

44. Turner, W. A.: Optic Atrophy Associated with Pernicious Anemia, *Brain* **63**:225, 1940.

ticular relation between visual failure and the degree of anemia. The differential diagnosis of tabetic optic atrophy, compression optic atrophy, scotomas due to cerebral tumors, Leber's disease occurring late in life and tobacco amblyopia is discussed. The author recommends that the blood and the gastric secretions be examined for evidence of pernicious anemia in patients with bilateral optic atrophy occurring in middle life for which no adequate cause can be found. He considers that the prognosis for return of vision is good if the patients are treated early with injections of liver extract. Improvement is slow and may not be quite complete. The cause of the optic atrophy is considered by the author to be a deficiency of some unidentified factor which is present in liver, and the process may be similar to that observed in subacute combined degeneration of the spinal cord.

From a review of the literature Wiltrakis and Partipilo<sup>45</sup> conclude that mild mental changes occur in 35 to 40 per cent of patients with pernicious anemia, consisting of indolence, apathy, irritability, slight confusion and depression. In 4 to 7 per cent, more pronounced aberrations or psychoses are observed. Over a period of seven years, from 1931 to 1938, the authors observed 24 persons with pernicious anemia among the mentally ill patients at the Elgin State Hospital, Elgin, Ill., an incidence of 0.18 per cent. In 8 of the 24 patients pernicious anemia was thought to be incidental, and in 16 it was considered that the anemia was definitely related to the mental changes. No characteristic reaction pattern was noted, but according to the literature and in the patients observed, paranoid and confused states and depressive features predominated. Irritability was a prominent symptom. The prognosis in this type of psychosis is poor, but the patients should be given the benefit of prolonged and intensive anti-pernicious-anemia therapy. DeNatale<sup>46</sup> gives a review of the literature pertaining to the mental changes in patients with pernicious anemia and presents 5 illustrative cases encountered at the Hudson River State Hospital, Poughkeepsie, N. Y. He concludes that there does not appear to be any well defined mental syndrome associated with pernicious anemia, but the symptom complexes characterized by irritability, suspiciousness, ideas of reference and well defined paranoid formulations are most commonly encountered. Causes are generally found, either psychogenic or external, which in themselves would be sufficient to produce mental illness. Pernicious anemia per se may be considered as only an aggravating factor in the production of the psychosis. In his opinion, the prognosis in these disturbances is the

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45. Wiltrakis, G. A., and Partipilo, A. V.: Psychoses with Pernicious Anemia, Elgin State Hosp. Papers 4:166, 1941.

46. DeNatale, F. J.: Psychotic Manifestations Associated with Pernicious Anemia, Psychiatric Quart. 15:143, 1941.

same as that in the reaction-types encountered without evidence of physical disease.

Evans,<sup>47</sup> Emmett and Beare,<sup>48</sup> Nesbit and Gordon<sup>49</sup> and Rose<sup>50</sup> have all contributed articles dealing with the neurogenic bladder which are, therefore, of interest to those concerned with the management of patients with pernicious anemia, in whom bladder complications frequently occur.

An excellent discussion of the more important points regarding the cause of the changes in the nervous system in pernicious anemia and their treatment is given by Woltman and Heck.<sup>51</sup> They emphasize that early and efficient treatment is essential if irreparable damage to the nervous system is to be avoided. The most effective form of therapy, they agree, is the parenteral administration of liver extract, although they are not prepared to express themselves regarding the relative merits of the cruder and the more refined preparations. Apparently good results were observed after the use of either type when an adequate dose was employed. The intensity of the symptoms referable to the nervous system is not a criterion of the prognosis in their opinion, but of much greater importance is the duration of the manifestations. In general, it may be stated that after two years there is a steadily decreasing prospect of improvement. Some authors believe, however, that symptoms may diminish even after they have been present for as long as four years. Experience demonstrates that about 86 per cent of all patients with involvement of the nervous system will show evidence of improvement after adequate therapy and that this is most likely to occur after the third to the sixth month of therapy in those whose condition could be classified as mild or moderately severe. It should be noted, however, that a high degree of functional recovery may occur even when the pathologic changes are extensive. Although animal experimentation suggests that vitamin B may be related to the cause of the lesions of the nervous system, the authors are not in accord with those who believe that the administration of brewers' yeast is helpful, and after a trial they discarded it as a therapeutic agent. Careful attention is given to the various conditions which may cause combined degeneration similar to that

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47. Evans, J. P.: The Physiologic Basis of Neurogenic Bladder, *J. A. M. A.* **117**:1927 (Dec. 6) 1941.

48. Emmett, J. L., and Beare, J. B.: Bladder Difficulties of Tabetic Patients, with Special Reference to Treatment by Transurethral Resection, *J. A. M. A.* **117**:1930 (Dec. 6) 1941.

49. Nesbit, R. M., and Gordon, W. G.: The Surgical Treatment of the Autonomous Neurogenic Bladder, *J. A. M. A.* **117**:1935 (Dec. 6) 1941.

50. Rose, D. K.: The Urinary Bladder: Normal, Myogenic and Neurogenic, *J. Urol.* **46**:257, 1941.

51. Woltman, H. W., and Heck, F. J.: Treatment of Neurologic Changes Complicating Pernicious Anemia, *Minnesota Med.* **24**:653, 1941.

observed in pernicious anemia. A survey of the literature suggests that such a picture can be produced by chronic alcoholism, gastric carcinoma, obstruction and fistulas of the intestinal tract, the so-called prepernicious anemia and possibly scurvy. Less likely, but possibly, it may be associated with pancreatitis, pellagra, hemolytic icterus, amyotrophic lateral sclerosis and certain unclassified diseases. It is entirely possible that in all cases typical subacute combined degeneration of the spinal cord, of the type seen in pernicious anemia, may be due to one underlying cause, presumably nutritional and in the nature of a deficiency state. This, according to the authors, may perhaps be an absence of Castle's intrinsic factor. In an effort to shed some light on the common cause of combined degeneration of the cord, approximately 2,000 cases were reviewed and careful consideration was given to the 77 in which free hydrochloric acid was present in the gastric secretions. Of these 77 cases, there were 8 in which signs of involvement of the posterior and the lateral columns of the spinal cord were present, and in addition, there was a symmetric, persistent paresthesia of the hands and feet. The clinical picture presented, therefore, was exactly similar to that observed in association with pernicious anemia except for the presence of free hydrochloric acid. In 5 of these 8 cases there was evidence of a nutritional deficiency which may have been the etiologic factor responsible for the lesions of the nervous system. In the remaining 3 cases there was no indication that this was so. The authors believe that they can distinguish subacute combined degeneration of the spinal cord as seen in pernicious anemia from other types of "combined sclerosis" by the association with the former of persistent, symmetric paresthesia; impaired vibratory sense, and evidence of symmetric involvement. They discuss the question of peripheral nerve disturbances and conclude that such lesions contribute to the clinical picture, but to a limited degree only. A study by Davison<sup>52</sup> of 10 patients with pernicious anemia and subacute combined degeneration of the cord who received liver showed that subjective improvement occurred in all patients except 1 whose condition could not be evaluated because he was seen only once. Moreover, there was evidence of objective improvement in 3 of the 10 patients. Davison stresses that improvement in the neurologic manifestations of pernicious anemia may be due to amelioration of the general condition coincident with the disappearance of the anemia or to a reduction or destruction of the hypothetical toxin which affects the myelin sheaths and axis-cylinders. He considers, from observations made on a series of 10 patients, that the myelin sheaths are first attacked. Once the axis-cylinders are destroyed, their regeneration is problematic. An intense gliosis or glial productivity of the involved

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52. Davison, C.: Effect of Liver Therapy on Pathways of Spinal Cord in Subacute Combined Degeneration, *Arch. Int. Med.* **67**:473 (March) 1941.



pathways in the treated patients, in contrast to the poor gliosis which he observed in those who were untreated, is attributed to a reduction in the amount of potency of the hypothetic toxin.

Zillhardt and his associates<sup>53</sup> state that despite adequate liver therapy, certain residual neural manifestations are likely to remain in patients with pernicious anemia and changes in the spinal cord. It was the purpose of their studies to determine what relation, if any, the administration of vitamin B<sub>1</sub> might have on the neurologic changes in patients who had been treated adequately with liver extract over a period of time. Treatment with liver alone caused a striking initial improvement in the disturbances in the nervous system. When the neurologic status became stationary, a number of these patients were given thiamine intramuscularly or orally, whereas others served as a control group, with only liver therapy continued. The authors' observations led them to conclude that thiamine might have a beneficial effect on the residual manifestations in the nervous system. Of the two preparations of thiamine hydrochloride employed, 3,000 international units of one administered intramuscularly three times a week was more effective than 900 international units of the other given orally twice daily. The maximum beneficial effect appeared to occur during the first two months of therapy, after which there was no further change. An additional study<sup>54</sup> was made on 7 patients who were given 1 cc. of a preparation of vitamin B complex intramuscularly three times a week for three months, in addition to adequate liver therapy. It was concluded that with the exception of some improvement in the sense of well-being, the group which received the vitamin B complex intramuscularly showed little change in subjective and in objective signs in comparison with the control group.

Mussio Fournier and Rawak<sup>55</sup> report the case of a 54 year old woman with subacute combined degeneration of the spinal cord who improved strikingly after the administration of raw liver by mouth and injections of liver extract and vitamin B<sub>1</sub>. The authors believe that vitamin B<sub>1</sub> is specific in the treatment of the neurologic complications of pernicious anemia and that the most satisfactory results are observed in patients who are treated early.

A group of patients with the neurologic manifestations of pernicious anemia, consisting of 19 men and 8 women between the ages of 35 and

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53. Zillhardt, J. C.; MacLean, K., and Murphy, W. P.: Effect of Thiamine on Residual Neural Disturbances of Treated Pernicious Anemia, *Ann. Int. Med.* **15**:33, 1941.

54. Zillhardt, J. C.; Howard, I., and Murphy, W. P.: Effect of Vitamin B Complex on Residual Neural Disturbances of Treated Pernicious Anemia, *Ann. Int. Med.* **15**:44, 1941.

55. Mussio Fournier, J. C., and Rawak, F.: Acción terapéutica de la vitamina B<sub>1</sub> en la mielosis funicular de la anemia perniciosa, *Arch. Clin. e Inst. endocrinol.* (fasc. 2) **1**:637, 1937-1940.

65 years, was studied by Rubegni.<sup>56</sup> The evidences of involvement of the spinal cord varied from spastic paraplegia to simulation of tabes dorsalis and included peripheral types similar to various forms of polyneuritis and cerebral forms manifesting themselves by mental disturbances. After the administration of liver orally or parenterally a striking improvement resulted in all cases, except in instances of advanced lesions. In most instances the patients were able to resume work with only minor residual manifestations persisting. The author considers that liver therapy is of value especially when the liver is administered in large doses, over long intervals and before the lesions in the nervous system become advanced.

Street and his co-workers<sup>57</sup> have made a careful study of long-continued subminimal vitamin B<sub>1</sub> deficiency in dogs. According to them, the earlier literature on the subject may be summarized as follows: Vitamin B<sub>1</sub> deficiency causes myelin degeneration of peripheral nerves, and sometimes in the spinal cord, in several species of laboratory animals. In most instances the diets employed were deficient with respect to the entire vitamin B complex. More recent studies have suggested that the lesions due to vitamin B<sub>1</sub> deficiency may be central rather than peripheral. The authors observed dogs in which the stores of vitamin B<sub>1</sub> had been depleted and which were maintained in a state of subnutrition for seventy-six to two hundred and ninety-three days with exceedingly small amounts of vitamin B<sub>1</sub>. There developed a condition of moderate spasticity of the hindlegs, unsteadiness, staggering and vomiting. Histologic examination of the nervous system revealed extensive myelin degeneration both of peripheral nerves and of the posterior columns. This would appear to be due chiefly to the lack of vitamin B<sub>1</sub> in the tissues, rather than to inanition accompanying the deficiency state. The reviewers wish to emphasize that, as recent studies by Field, Robinson and Melnick<sup>58</sup> suggest, this vitamin is not absorbed normally in the presence of achlorhydria, which may be a factor in the production of at least part of the syndrome of subacute combined degeneration of the spinal cord in patients with pernicious anemia.

*Sensitivity to Liver Extract.*—The subject of sensitivity to parenterally administered liver extract is discussed by Bynum,<sup>59</sup> and reference is made to six other articles dealing with this subject. He states that

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56. Rubegni, R.: Considerazioni cliniche sulle complicazioni neurologiche in corso di anemia perniciosa, Policlinico (sez. med.) **48**:167, 1941.

57. Street, H. R., and others: Some Effects Produced by Long Continued Subminimal Intakes of Vitamin B<sub>1</sub>, Yale J. Biol. & Med. **13**:293, 1941.

58. Field, H., Jr.; Robinson, W. D., and Melnick, D.: Vitamins in Peptic Ulcer, Ann. Int. Med. **14**:588, 1940.

59. Bynum, W. T.: Allergy to Liver Extract, J. Oklahoma M. A. **34**:55, 1941.

the condition usually develops in patients who have received injections for some time or in patients who, after weeks or months of treatment, discontinue injections for a short period and then resume them. He cites Crip as stating that an organ, rather than a species, sensitivity, is involved. The patients whom Crip studied were susceptible to sheep, beef, and pork liver extract given either intramuscularly or intradermally. When they were tested with muscle protein extracts from these same species, reactions were not observed. In the case reported by Bynum the patient had typical allergic reactions when liver preparations were given, characterized by massive generalized urticaria, dyspnea and pronounced swelling of the tongue; the reactions were promptly relieved by the administration of 5 minims (0.31 cc.) of a 1:1,000 solution of epinephrine hydrochloride. The patient was sensitive to many commercial liver preparations for parenteral or oral administration, and an attempt at desensitization by the administration of divided doses was unsuccessful. A deaminized liver product said to be free from protein and histamine was finally employed, and no manifestations of sensitivity were observed. Andrews<sup>60</sup> also reports an instance of sensitivity to liver extract, in which satisfactory desensitization was accomplished by injecting doses of increasing size on successive days. The author emphasizes the following points: The allergic state usually appears in patients who have had a number of injections of liver extract without ill effect; changing the brand of extract has not prevented the attacks; any possible allergic manifestation, however mild, is an indication for caution in the administration of the next dose and suggests the advisability of a preliminary cutaneous test; desensitization may be effected in some cases, and it is usually advisable to start with small intradermal doses.

*Miscellaneous Observations Concerning Pernicious Anemia.*—Neal<sup>61</sup> gives a résumé of present knowledge relating to the diagnosis of pernicious anemia and emphasizes the importance of recognizing the disease in an early stage. He has devised an ingenious mechanical chart on which are listed twelve different types of positive diagnostic information. He states that for some patients all types may be supplied but that a score of 66 per cent indicates the possible or probable presence of pernicious anemia, whereas one of 40 per cent merely suggests that the presence of the disease should be suspected. We cannot advocate any such mechanical method for the diagnosis of pernicious anemia, since it gives equal weight to all twelve types of information, some of which are of no clinical importance. There are other points in the article with which we do not agree. For instance, it is difficult to believe that true

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60. Andrews, C. T.: Allergic Reaction to Liver Extract, *Lancet* 1:664, 1941.

61. Neal, M. P.: Diagnosis of Pernicious Anemia, *J. Missouri M. A.* 38: 316, 1941.

addisonian pernicious anemia has been shown to occur in a full-blooded Negro, although it has been observed frequently in mulattoes.

Pernokis and Freeland <sup>62</sup> report the results of chemical determinations performed on the blood of 15 patients with pernicious anemia in a state of relapse. The values for total lipoids were much above normal, but those for fatty acids, "lecithins" and lipid phosphorus were greatly diminished. Cholesterol was present in slightly diminished or normal amounts, and the distribution between the free and the esterized form was normal. In only one of six determinations of amino acid was there an increase, while in the others it was within normal limits. The determination of calcium, phosphorus, uric acid, creatinine, sugar, chloride, carbon dioxide, inorganic sulfates, ethereal sulfates, total proteins, albumin, and globulin gave normal results. All nonprotein and urea nitrogen estimations yielded results within normal limits except in 1 patient. Results of four rose bengal hepatic function tests showed dye retention, and the result of the fifth was normal. The icterus index was increased in about three fourths of the patients. The basal metabolic rate was above normal in 80 per cent of the patients. One glutathione determination done on a patient with a severe degree of anemia showed 14.5 mg. of reduced glutathione and none of the oxidized form per hundred cubic centimeters. This patient died two days later, and at necropsy a section taken from the liver and extracted with solution of sodium chloride showed 168.7 mg. of reduced glutathione per hundred grams of liver. No oxidized glutathione was demonstrated in the saline liver extract.

A case is reported by Markowitz <sup>63</sup> of severe macrocytic anemia, which he attributes to bone metastases from an adenocarcinoma of the stomach. Bone marrow obtained at necropsy was bright red, interspersed with small, purple-gray areas. On microscopic examination, large groups of tumor cells, with no definite arrangement, were seen invading the bone.

Sterne, Schiro and Molle, <sup>64</sup> after a review of the literature, conclude that most of the cases of disease designated as leukanemia must be rejected as failing to fulfil the requisites for the diagnosis of both pernicious anemia and leukemia. There can be no doubt, however, that a few well substantiated cases have been observed in which the two diseases have coexisted simultaneously in the same persons. The authors report the case of a woman, 57 years of age, who had a severe macrocytic

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62. Pernokis, E. W., and Freeland, M. R.: Blood Chemistry Determinations in Pernicious Anemia, *J. Lab. & Clin. Med.* **26**:1177, 1941.

63. Markowitz, B.: Bone Carcinomatosis Simulating Pernicious Anemia: A Case Report, *Illinois M. J.* **80**:296, 1941.

64. Sterne, E. H., Jr.; Schiro, H., and Molle, W. E.: Pernicious Anemia Complicated by Myelogenous Leukemia, *Am. J. M. Sc.* **202**:167, 1941.

anemia which responded promptly to liver extract. Four and one-half years later the patient died, and necropsy disclosed chronic myeloid leukemia and posterior (and suggestive lateral) degenerative changes in the spinal cord. The authors conclude that until further evidence is available concerning the fundamental defect in leukemia, such an association must be considered merely fortuitous.

#### HYPOCHROMIC ANEMIAS

*Hypochromic and Microcytic Anemia in Adults.*—The subject of chlorosis is discussed by Olef,<sup>65</sup> who reports observations made on 8 patients. He emphasizes the occurrence of thrombocytosis in them, a finding in contrast to the low platelet counts usually encountered in persons with pernicious anemia and idiopathic hypochromic anemia. Four of the author's patients exhibited histamine-refractory achlorhydria; the others had various degrees of hypochlorhydria. He concludes that chlorosis is a distinct disease entity and that the severe form is rare, but that milder forms are common. Olef proposes as a substitute for chlorosis the term hypochromic iron deficiency anemia of adolescence, frequently associated with achlorhydria. However, the very attempt at comprehensiveness which this designation implies makes it inadequate, since the disorder is also frequently associated with endocrine dysfunction, unrecognized hypermenorrhea and nutritional deficiency.

Chlorosis has also been made the subject of a communication by Alsted.<sup>66</sup> He reports 6 cases of the disease encountered during a period of ten years in Medical Department B, Frederiksberg Hospital, Copenhagen, Denmark. His patients were somewhat older than the majority of patients in the cases of chlorosis reported in the past. He suggests nutritional deficiency as a possible etiologic factor and regards as probably significant the fact that in two thirds of his cases the patients were admitted during the darkest season of the year. Alsted employs the following criteria for the diagnosis of chlorosis: hypochromic anemia which responds to iron therapy, absence of pathologic bleeding, absence of severe gastrointestinal disorders and presence of hydrochloric acid in the gastric secretions. He suggests that the term essential juvenile iron deficiency anemia replace chlorosis. We object to the designation essential in describing the type of anemia under consideration, since its use might tend to discourage search for etiologic factors, which, in our opinion, can usually be found. The exclusion of patients with achlorhydria from the group with the disorder under discussion seems to us arbitrary, since the presence of gastric hydrochloric acid was

65. Olef, I.: Chlorosis, *New England J. Med.* **225**:358, 1941.

66. Alsted, G.: Chlorosis: Essential Juvenile Iron Deficiency Anemia, *Am. J. M. Sc.* **201**:1, 1941.

certainly not a universal finding in cases of classic chlorosis, nor does such a limitation appear to further the understanding of the pathogenesis of this disorder.

Four patients with dysphagia and anemia were examined roentgenologically by Johnstone.<sup>67</sup> In each an obstruction was found in the postcricoid region. The roentgen diagnoses were subsequently confirmed by endoscopy, although in 1 patient malignant changes in the adjacent mucosa were also observed.

Two interesting cases of hypochromic anemia associated with interstitial cystitis, or Hunner's ulcer, are reported by Robb.<sup>68</sup> In the first case the patient was a woman aged 57 who was believed to have suffered with hypochromic anemia for as long as twenty years. During the last six years of her illness she had experienced severe symptoms referable to the bladder. The diagnosis of Hunner's ulcer was made, and partial cystectomy was performed. The aforementioned symptoms persisted, however, until iron therapy was instituted, when they disappeared completely. In the second case the patient was a woman aged 48 who had hypochromic anemia of many years' standing, dysphagia, a pre-cancerous buccal lesion and interstitial cystitis with severe urinary symptoms. The author draws an analogy between the lesions of the bladder observed in these patients and the buccopharyngeal changes encountered frequently in patients with chronic hypochromic anemia.

The association of gastric secretory abnormalities and anemia is emphasized by Sandorf and Davidhoff,<sup>69</sup> who report a number of cases illustrating this relation. They suggest the term *achylia gastrica anemia* as a designation for addisonian pernicious anemia and the name *achlorhydric anemia* for hypochromic anemia associated with absence of hydrochloric acid but not of gastric enzymes.

Two cases of primary, or idiopathic, hypochromic anemia terminating in pernicious anemia which are reported by Miller and Dameshek<sup>22</sup> have already been discussed in the section "Relation Between Pernicious Anemia and Other Diseases." In both cases the patients were females who were known to have had hypochromic anemia with achlorhydria for a number of years before the hematologic features of pernicious anemia developed. A specific therapeutic response was obtained in each instance.

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67. Johnstone, A. S.: Some Radiological Observations on Post-Cricoid Obstruction and Anaemia, *Brit. J. Radiol.* **14**:177, 1941.

68. Robb, D.: Two Cases of Hunner's Ulcer of Bladder or Interstitial Cystitis in the Presence of Idiopathic Hypochromic Anaemia, *Australian & New Zealand J. Surg.* **10**:393, 1941.

69. Sandorf, M., and Davidhoff, M.: Gastric Anemia Syndromes, *M. Bull. Vet. Admin.* **17**:366, 1941.

A case of advanced gout of twenty-eight years' duration occurring in a male and associated with chronic alcoholism and extremely severe hypochromic anemia is reported by Lambie and Davies.<sup>70</sup> There was no history of loss of blood. The patient died in cardiac decompensation, and necropsy was performed.

Hematologic studies were carried out by McIntosh and Morris<sup>71</sup> on 1,059 residents of Glasgow, Scotland, who were receiving public assistance. Hypochromic anemia was prevalent in children below the age of 4 years and in women during the reproductive period of life. The incidence of anemia was low in school children, in men and in women above the age of 50. In children important etiologic factors were inadequate intake of iron, low birth weight and probably recurring infections of the respiratory tract. Pregnancy, childbirth, lactation and, to a less extent, menorrhagia were considered of importance in causing anemia in women. The authors observed an inverse relation between the hemoglobin level and the dose of iron required for a satisfactory hemopoietic response.

Further investigations of the anemia prevalent among coolies working in Indian tea gardens are reported by Hare.<sup>72</sup> He concludes that deficiencies of vitamins, animal protein and calcium are all of importance in the causation of such anemia and account for the large incidence of low hemoglobin levels in growing children.

Of 364 college women examined by Pryor and Ferguson,<sup>73</sup> 145 had hemoglobin levels which the authors considered below the normal range. Dysmenorrhea was commonly associated with anemia, and the incidence of low hemoglobin values was greater among young women of linear constitution. A group of 100 female students between the ages of 15 and 23 was studied by Sister Mary Alcuin Arens<sup>74</sup> with particular reference to the status of the blood and the gastric secretion of hydrochloric acid. No statistically significant correlation between these values was established.

Few important contributions to the therapy of hypochromic anemia have appeared during the past year. Eleven patients suffering with peptic ulcer and hypochromic anemia were treated by Ehrenfeld and

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70. Lambie, C. G., and Davies, G. F. S.: Case of Chronic Gout with Anaemia, *M. J. Australia* **1**:701, 1941.

71. McIntosh, J., and Morris, N.: Anaemia in the Poor of Glasgow: Incidence, Aetiological Factors and Treatment, *Glasgow M. J.* **136**:103, 1941.

72. Hare, K. P.: On the Importance of Malnutrition in the Aetiology of the Anaemic State in Tea Garden Coolies, *Indian M. Gaz.* **76**:531, 1941.

73. Pryor, H. B., and Ferguson, M.: Anemia in College Women, *Northwest. Med.* **40**:58, 1941.

74. Arens, Sister M. Alcuin: A Study of Hematopoiesis in a Group of Female Students Ages Fifteen to Twenty-Three Years Through a Study of Gastric Secretions and Correlated Blood Counts, *Am. J. M. Technol.* **7**:202, 1941.

Wallace<sup>75</sup> with an antacid consisting of a mixture of iron and aluminum hydroxides. The dose employed supplied daily 0.24 Gm. of iron, or the iron equivalent of slightly more than 1.0 Gm. of ferrous sulfate. Satisfactory hemoglobin regeneration without evidence of gastric irritation was observed in patients receiving this form of therapy.

In 27 active professional blood donors Santy<sup>76</sup> compared hemoglobin regeneration during periods in which medicinal iron was given and that during others in which it was withheld. The preparation used was ferrous sulfate in a dose of 0.2 Gm. three times a day. The author reports that hemoglobin regeneration after blood donation took place eight times more rapidly when iron therapy was instituted. The return to the predonation hemoglobin level after withdrawal of 500 cc. of blood was complete in an average of eleven days in the case of iron-treated donors.

Several articles dealing with the therapy of hypochromic anemia have been contributed by Fowler and Barer.<sup>77</sup> One group of patients with mild anemia was treated with 1 Gm. of iron and ammonium citrates daily, and to another series with similar hemoglobin levels 1 Gm. of reduced iron U. S. P. was administered daily. Treatment in every instance was discontinued after sixty days. Increases in hemoglobin were observed in all of the patients, attaining a maximum value at the end of ten weeks and subsequently declining to the pretreatment level, usually after the lapse of twenty-six weeks. Other comparable subjects were treated in the same manner except that iron therapy was not discontinued. The same rise and subsequent fall of the hemoglobin level was observed in these patients, in spite of uninterrupted medication. Twelve healthy males possessing high hemoglobin values were treated in a similar manner. In these subjects also the hemoglobin values increased, although in relatively slight degree, and later declined. The data reported give support to the opinion expressed in the past by many authors that medicinal iron possesses a stimulant action in hemopoiesis in addition to its role in replacement therapy. Fowler and Barer report that the effects of relatively small doses of iron and ammonium citrates on hemoglobin formation by adults with mild hypochromic anemia were not enhanced by supplements of copper sulfate.

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75. Ehrenfeld, I., and Wallace, R. P.: Iron as Therapeutic Supplement in Peptic Ulcer Therapy, *Am. J. Surg.* **53**:470, 1941.

76. Santy, A. C.: The Response of Blood Donors to Iron, *Am. J. M. Sc.* **201**:790, 1941.

77. Fowler, W. M., and Barer, A. P.: Some Effects of Iron on Hemoglobin Formation, *Am. J. M. Sc.* **201**:642, 1941; Effect of Copper and Iron on Hemoglobin Regeneration, *J. Lab. & Clin. Med.* **26**:832, 1941. Barer, A. P., and Fowler, M. W.: Comparison of Hemoglobin Response to Varying Dosages of Iron, *ibid.* **26**:1482, 1941. Fowler, W. M., and Barer, A. P.: Etiology and Treatment of Iron Deficiency Anemias, *J. Iowa M. Soc.* **31**:420, 1941.



The question of the relation of vitamin C deficiency to iron metabolism and hypochromic anemia has been reopened in two papers. Lozner<sup>78</sup> observed 5 persons with presumptive vitamin C deficiency as evidenced by absence of reduced ascorbic acid in the blood plasma. Three of the patients exhibited clinical signs of scurvy; 1 suffered with pellagra, and 1 had idiopathic hypochromic anemia. The diet supplied during the period of observation was low in vitamin C and the vitamin B complex. In 4 of the patients hemoglobin increases occurred spontaneously or in response to iron medication. The author concludes that hemoglobin regeneration may occur in the absence of reduced ascorbic acid from the blood plasma, as determined by chemical test.

Liu and associates<sup>79</sup> conducted a survey of 238 Chinese boys between the ages of 11 and 20 who were inmates of a municipal institution. Over one half of the subjects were anemic. Sixteen boys suffering with anemia were studied in detail. Eight were given 50 mg. of ascorbic acid daily for four weeks. The other 8 boys received 1.5 Gm. of ferrous carbonate daily for the same length of time. Although in the former group the administration of ascorbic acid was accompanied by an increase in the plasma content of ascorbic acid from an average of 0.23 to an average of 0.91 mg. per hundred cubic centimeters, no effects were observed either on the hemoglobin content or on the hematocrit reading. In the latter group the institution of iron therapy was followed in most cases by significant increases in red cell count, hemoglobin content and hematocrit reading, although the subnormal value of the plasma ascorbic acid persisted unchanged. The authors conclude that whereas anemia is commonly associated with vitamin C deficiency, the first-named disorder, in all probability, is due to a concomitant deficiency of iron.

Blood studies made on 4,644 private patients revealed an incidence of hypochromic anemia in 38 per cent, according to a report by Bunce and his associates.<sup>80</sup> The ratio of females to males with iron deficiency anemia was 4:1. The important etiologic factors included chronic loss of blood, poor diet, gastric anacidity, hypothyroidism, pregnancy and chronic infections.

A form of familial microcytic anemia refractory to all forms of therapy employed is described by Strauss, Daland and Fox.<sup>81</sup> The

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78. Lozner, E. L.: Studies on Hemoglobin Regeneration in Patients with Vitamin C Deficiency, *New England J. Med.* **224**:265, 1941.

79. Liu, S. H., and others: Anemia in Vitamin C Deficiency and Its Response to Iron, *Proc. Soc. Exper. Biol. & Med.* **46**:603, 1941.

80. Bunce, A. H.; Dougherty, M. S., Jr., and Davis, R. C.: Clinical Studies of Secondary Anemia, *J. M. A. Georgia* **30**:457, 1941.

81. Strauss, M. B.; Daland, G. A., and Fox, H. J.: Familial Microcytic Anemia: Observations on Six Cases of a Blood Disorder in an Italian Family, *Am. J. M. Sc.* **201**:30, 1941.

disorder was observed in 6 members of an Italian family. There was no evidence of increased hemolysis; the resistance of the erythrocytes to hypotonic solution of sodium chloride was greater than normal, and no increase of the serum bilirubin or the urine urobilinogen was observed. The red cells were small; the mean corpuscular hemoglobin content was correspondingly low, and the mean corpuscular hemoglobin concentration was nearly normal. Roentgen examination of the skulls of the subjects revealed a granular appearance. The disorder was inherited as a mendelian dominant.

A review of the present status of iron therapy has been written by Nelson.<sup>82</sup> He emphasizes the superior therapeutic properties of ferrous preparations. Much of importance is contained in an article by Kruse and Butler<sup>83</sup> dealing with vitamin and mineral deficiencies. An interesting account of the origin and early use of Blaud's pills (ferrous carbonate) has been published by Neuroth and Lee.<sup>84</sup> Fisher and Peabody<sup>85</sup> observed that ferrous sulfate fails to oxidize when dissolved in aqueous liver extract. From 50 to 95 per cent of ferric iron added to liver extract underwent reduction to the ferrous state. The author suggests that the efficacy of combinations of liver extract and iron salts in the treatment of hypochromic anemia may be partly due to the action of the liver extract in supplying or maintaining iron in the bivalent form. Clarke's formula for an inexpensive easily prepared and relatively stable syrup of ferrous sulfate is reported by an anonymous author.<sup>86</sup> The stability of the preparation is maintained by its content of citric acid and simple syrup.

*Hemopoiesis and Nutritional Anemia in Children.*—A valuable contribution by Gilmour<sup>87</sup> described the embryonic development of human blood vessels and cells up to the establishment of a complete circulation. For this phase of the work the author had access to a large number of presomite and somite embryos. The later development of the cells of the blood from the fourth week of intrauterine life until birth is also described in detail. Shapiro and Bassen<sup>88</sup> report results of peripheral blood studies

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82. Nelson, E. E.: Iron, *Internat. M. Digest* **38**:311, 1941.

83. Kruse, H. D., and Butler, A. M.: Round Table Discussion on Vitamin and Mineral Deficiencies, *J. Pediat.* **18**:128, 1941.

84. Neuroth, M. L., and Lee, C. O.: A History of Blaud's Pills, *J. Am. Pharm. A. (Scient. Ed.)* **30**:60, 1941.

85. Fisher, R. S., and Peabody, W. A.: Ferrous and Ferric Iron in Liver Extracts, *Proc. Soc. Exper. Biol. & Med.* **46**:207, 1941.

86. A Stable Syrup of Ferrous Sulfate, *J. Am. Pharm. A. (Prac. Pharmacy Ed.)* **2**:4, 1941.

87. Gilmour, J. R.: Normal Haemopoiesis in Intra-Uterine and Neonatal Life, *J. Path. & Bact.* **52**:25, 1941.

88. Shapiro, L. M., and Bassen, F. A.: Sternal Marrow Changes During the First Week of Life: Correlation with Peripheral Blood Findings, *Am. J. M. Sc.* **202**:341, 1941.

and examinations of aspirated sternal marrow performed on 35 normal full term infants during the first twenty-four hours of life and again one week later. Moderate declines in erythrocyte counts and hemoglobin values and sharp falls in reticulocyte and leukocyte counts were observed. At the end of the first week a change had occurred from myeloid to lymphocytic predominance in the white cells of the circulating blood. A significant decrease in the erythroid elements of the sternal marrow, with diminished erythropoiesis, was noted during the first week of life.

The placentas obtained from 260 women, of whom 200 were at full term, were examined by Anderson<sup>89</sup> with reference to the percentage incidence of nucleated erythrocytes. One thousand red cells were counted within the lumens of the chorionic capillaries, and the ratio of nucleated to nonnucleated cells were ascertained. The author found that up to the sixth or the seventh week of gestation practically all of the erythrocytes observed were nucleated, by the twelfth week less than 1 per cent of nucleated forms were found and in 83.5 per cent of full term pregnancies counts of 1,000 red cells were made without the observation of a single nucleated erythrocyte.

The blood values of 15 healthy institutionalized infants were determined by Washburn.<sup>90</sup> The author suggests that the observed decreases in erythrocyte count, hemoglobin level and packed cell volume occurring during the first six to nine weeks are due to two causes: rapid increase in total body mass, with a parallel increase in the plasma volume and consequent dilution of the red cell mass, and abrupt decrease in reticulocytes, indicating a sudden decline in production of erythrocytes to an extent insufficient for the maintenance of the original red cell level. A rise in the number of reticulocytes occurs at about the fifth to the eighth week of life, followed by increases in the erythrocyte count and the hemoglobin level. It is believed by the author that the period of accelerated erythropoiesis is brought about in response to the stimulus of oxygen lack. The postnatal hemopoietic adjustment period for most healthy babies appears to extend throughout the first fifteen to twenty weeks of life.

Hematologic standards for healthy newborn infants have been devised by Chuinard, Osgood and Ellis.<sup>91</sup> The effects of early clamping of the cord and consequent deprivation of the infant of placental blood have

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89. Anderson, G. W.: Studies on Nucleated Red Cell Count in Chorionic Capillaries and Cord Blood of Various Ages of Pregnancy, *Am. J. Obst. & Gynec.* **42**:1, 1941.

90 Washburn, A. H.: Blood Cells in Healthy Young Infants: Postnatal Readjustments of the Red Blood Cells in Individual Babies, *Am. J. Dis. Child.* **62**:530 (Sept.) 1941.

91. Chuinard, E. G.; Osgood, E. E., and Ellis, D. M.: Hematologic Standards for Healthy Newborn Infants, *Am. J. Dis. Child.* **62**:1188 (Dec.) 1941.

been studied extensively by Windle and his associates.<sup>92</sup> These investigators found that the erythrocyte count and the hemoglobin level at birth were unaffected by early or late tying of the umbilical cord. However, a difference was soon observed, and throughout the first week of life the average hemoglobin level of infants whose cords were tied late was 22.1 Gm. per hundred cubic centimeters in comparison to a value of 19.5 Gm. in the case of infants subjected to early clamping of the cord. The same authors submit evidence indicative of an average loss of 105 cc. of blood to the infant by tying of the cord immediately after birth. By calculation it is shown that such a loss can account for a negative difference of nearly 3 Gm. of hemoglobin per hundred cubic centimeters at 6 and at 9 months of age. The actual lowering of the hemoglobin value attributable to deprivation of placental blood, as observed in a group of 28 infants aged 8 to 10 months, was slightly greater than 1 Gm. per hundred cubic centimeters. The conclusion is reached that deprivation of placental blood may be an important factor in the development of iron deficiency anemia during the first year of life, and the practice of clamping the umbilical cord before pulsations have ceased is condemned.

The subject of anemias of early and of late infancy was discussed comprehensively at the tenth annual meeting of the American Academy of Pediatrics.<sup>93</sup> Strong<sup>93a</sup> defines anemia of prematurity as a physiologic anemia of an infant with an impaired anatomic and physiologic development and considers that lack of iron is not a factor in its causation. Windle<sup>93b</sup> finds no correlation between the incidence of maternal and of infant anemia. With this finding we are in disagreement, since we have observed iron deficiency anemia during the first year of life in the majority of infants born of mothers suffering with untreated hypochromic anemia during pregnancy.<sup>94</sup>

Two hundred and seventy-seven healthy infants living in the suburbs of Sydney, Australia, were studied by Cunningham<sup>95</sup> with respect to

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92. Windle, W. F.: Development of the Blood and Changes in the Blood Picture at Birth, *J. Pediat.* **18**:538, 1941. Wilson, E. E.; Windle, W. F., and Alt, H. L.: Deprivation of Placental Blood as Cause of Iron Deficiency in Infants, *Am. J. Dis. Child.* **62**:320 (Aug.) 1941. DeMarsh, Q. B.; Alt, H. L., and Windle, W. F.: The Effect of Depriving the Infant of Its Placental Blood on the Blood Picture During the First Week of Life, *J. A. M. A.* **116**:2568 (June 7) 1941.

93 (a) Strong, R. A.: Anemias of the Newborn Infant, in Round Table Discussion on Anemias of Infancy, *J. Pediat.* **18**:550, 1941. (b) Windle, W. F., in discussion on Abt, A. F.: Anemia of Late Infancy, Round Table Discussion on Anemias of Infancy, *ibid.* **18**:556, 1941.

94. Simpson Memorial Institute: Unpublished data.

95. Cunningham, N. C.: Nutritional Anaemia in Infancy: A Review of Two Hundred and Seventy-Seven Sydney Infants at the Age of Nine Months, *M. J. Australia* **2**:349, 1941.

the incidence of nutritional anemia. The average age of the subjects was 9 months; the average hemoglobin content was 11.5 Gm. per hundred cubic centimeters, and the average erythrocyte count was 4,330,000 per cubic millimeter. The incidence of nutritional anemia was 7.6 per cent. Twins and children born prematurely tended to exhibit hematologic values below the average. No correlation was apparent between the maternal and the infant hemoglobin levels, and no increased incidence of morbidity was encountered among the children with subnormal blood values. It should be pointed out that the nutritional status both of the mothers and of the infants comprising this series was generally superior to that encountered in large urban populations.

Two cases of congenital diaphragmatic hernia, in 1 of which the patient was suffering with extremely severe hypochromic anemia, are reported by Isizaka.<sup>96</sup> A dramatic response to parenteral liver therapy in the case of a 3 month old infant suffering with hyperchromic anemia is reported by Cole.<sup>97</sup> The general subject of the therapy of nutritional anemia in infancy is considered by Stewart<sup>98</sup> and McAlpine.<sup>99</sup> The latter author discusses various forms of medicinal iron suitable for administration to babies.

The relation of anemia to hookworm infection in children aged 6 to 14 years living in rural counties of North Carolina was studied by Brown and Otto.<sup>100</sup> Hookworm infection was demonstrated in 42 per cent of the subjects. There was no greater incidence of anemia in the group proved to be infected, but the hemoglobin levels of all the subjects were either subnormal or at the lower limits of normal. Hemoglobin deficiency was attributed to many factors, such as infection with hookworm or with malarial organisms and nutritional inadequacies.

The iron intake and excretion of healthy preschool children was measured by Porter.<sup>101</sup> The replacement of 1 ounce (28 Gm.) daily of plain farina by the same quantity of farina fortified with irradiated yeast failed to affect significantly the amount of iron retained by the subjects. In a series of children of Mexican origin Breazeale and Greene<sup>102</sup> found

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96. Isizaka, K.: Remarkable Anemia Due to Diaphragmatic Hernia: Report of One Infantile Case, *Tohoku J. Exper. Med.* **39**:370, 1941.

97. Cole, L.: Hyperchromic Anaemia in an Infant: Response to Liver Extract, *Lancet* **2**:759, 1941.

98. Stewart, W. B.: Treatment of Blood Dyscrasias in Infancy and Childhood, *J. M. Soc. New Jersey* **38**:401, 1941.

99. McAlpine, K. L.: Management of the Nutritional Anaemia of Infancy, *Canad. M. A. J.* **44**:386, 1941.

100. Brown, H. W., and Otto, G. F.: Hemoglobin and Reticulocyte Studies on Hookworm and Malaria Infected Children, *Am. J. Hyg., Sect. D* **33**:22, 1941.

101. Porter, T.: Iron Balances on Four Normal Pre-School Children, *J. Nutrition* **21**:101, 1941.

102. Breazeale, E. L., and Greene, R. A.: Normal Blood Counts of Mexican Children of Tucson, Arizona, *Southwestern Med.* **25**:116, 1941.

slightly lower erythrocyte counts and hemoglobin values than those reported for American children of corresponding age groups. Wiehl<sup>103</sup> found evidence of continuous changes in red cell counts and hemoglobin levels throughout adolescence. The subjects were from families of superior economic circumstances and ranged in age from 12 to 18 years. Detailed data are supplied, and the author concludes that in the evaluation of the blood status of growing children standards based on sex and the year of age should be employed. Leichsenring and her co-workers<sup>104</sup> examined the blood of 258 high school girls between the ages of 12 and 19 years. The results are tabulated as follows:

Hemoglobin content, Gm./100 cc.....	12.21 $\pm$ 0.8
Erythrocyte count, cells per cu. mm.....	4,150,000 $\pm$ 240,000
Leukocyte count, cells per cu. mm.....	7,340 $\pm$ 1,770
Reticulocytes, % .....	1.08 $\pm$ 0.65
Mean erythrocyte diameter, microns.....	7.9 $\pm$ 0.2

*Anemia in Pregnancy.*—Little of importance has been contributed during the past year to the literature on the subject of anemia in pregnancy. Etiologic factors responsible for lowered erythrocyte counts and hemoglobin levels during gestation are discussed by Sturgis.<sup>26</sup> He emphasizes the prevalence of anemia associated with the gravid state and points out the value of prophylactic and corrective therapy in combating iron deficiency and the importance of the diet of the pregnant woman, particularly with respect to its content of protein from animal sources.

Chemical and cellular studies of the blood were made by Mull and Bill<sup>105</sup> on 30 dispensary patients whose normal pregnancies were at term. The erythrocyte count averaged 3,780,000 per cubic millimeter; the hemoglobin content, 11 Gm. per hundred cubic centimeters, and the packed cell volume, 28.5 per cent. These values, particularly the last, are considerably below those reported earlier by Bethell. The authors were unable to detect a relation between the results of blood studies and the age or number of pregnancies of the subjects composing their series.

Four hundred and fifty-six pregnant women of low economic status were studied by Bibb<sup>106</sup> with reference to dietary deficiencies, serum

103. Wiehl, D. G.: Medical Evaluation of Nutritional Status: Hemoglobin and Erythrocyte Values for Adolescents in High Income Families, *Milbank Memorial Fund Quart.* **19**:45, 1941.

104. Leichsenring, J. M.; Donelson, E. G., and Wall, L. M.: Studies of Blood of High School Girls, *Am. J. Dis. Child.* **62**:262 (Aug.) 1941.

105. Mull, J. W., and Bill, A. H.: Blood Findings in Late Pregnancy, *J. Lab. & Clin. Med.* **26**:1487, 1941.

106. Bibb, J. D.: Protein and Hemoglobin in Normal and Toxic Pregnancies, *Am. J. Obst. & Gynec.* **42**:103, 1941.

protein levels, hemoglobin values and incidence of toxemia. Low values for serum protein were much more common among women with evidence of toxemia than in the series as a whole. The incidence of anemia appeared to be greatest after the fifth month of gestation and was usually hypochromic. The average daily intake of dietary iron was said to be 10 mg. An apparent relation existed between low hemoglobin values and low intake of protein but not between subnormal hemoglobin levels and dietary deficiencies of iron. Khan<sup>107</sup> studied the blood values and food consumption of 22 mothers of working class families. Twelve of the subjects were considered anemic, but the criterion of anemia accepted by the author, a hemoglobin level of 13 Gm. per hundred cubic centimeters, is undoubtedly too high. No relation was found between the hemoglobin values and the intake of protein, iron, copper or calcium.

*Iron Metabolism and Experimental Anemia.*—Much progress in the elucidation of the problems of absorption, transport, storage, utilization and excretion of iron and of the metabolism of intermediary iron-containing compounds within the body may be expected as its radioactive isotope becomes more generally available for clinical and experimental investigations. Only an occasional brief report dealing chiefly with limited observations on animals appears in the current literature. Balfour<sup>108</sup> observed that in a typical experiment a normal dog absorbed 1.3 per cent of a single dose of 130 mg. of iron containing the radioactive isotope. When the animal was made acutely anemic by removal of two thirds of its total circulating blood and twenty-four hours later was given an equal dose of iron, the percentage of absorption was the same, but when the dog's hemoglobin was allowed to return to a level near normal at the expense of its storage supply of iron, the absorption of an orally administered dose of the metal approximated 10 per cent. The author inferred from these observations that a tissue factor, possibly related to the content of iron in the intestinal mucosa, was responsible for the heightened absorption by the iron-depleted animal.

Moore, Roberts and Minnich<sup>109</sup> confirmed the observations of Balfour, Hahn, Whipple and their associates that iron-deficient dogs absorb a much greater proportion of orally ingested iron than do normal animals. They also found that normal dogs which had been subjected to one massive hemorrhage seven days before receiving iron absorbed quantities which closely approximated those absorbed by anemic animals.

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107. Khan, N. U.: Diet of Anaemic Women, *Lancet* 1:11, 1941.

108. Balfour, W. M.: Factors Regulating the Absorption of Iron in Dogs as Measured with the Radioactive Isotope, *Am. J. Path.* 17:438, 1941.

109. Moore, C. V.; Roberts, H., and Minnich, V.: A Study of the Selective Absorption of Iron with the Aid of Its Radioactive Isotope, *J. Clin. Investigation* 20:436, 1941.

The level of plasma iron was not the controlling factor which determined the extent of iron absorption. Ross and Chapin<sup>110</sup> observed that adults with normal blood and presumably adequate reserves of iron absorbed only small quantities of the radioactive isotope in contrast to the large amounts assimilated by patients with hypochromic anemia. Patients with untreated pernicious anemia, in whom presumably no iron deficiency existed, absorbed only negligible amounts of iron. The authors arrived at the same conclusion reached by Balfour, that the selective absorption of iron is controlled by the amount of tissue iron present in the gastrointestinal mucosa. Radioactive iron was fed to 2 cows by Erf,<sup>111</sup> and the percentage of orally administered iron secreted in the milk was measured during a seventy-two hour period. The values were 1.5 and 2.5 per cent, respectively, for the 2 animals. The blood content of radioactive iron was almost the same in the 2 cows despite the fact that the iron reservoirs of 1 of the animals had been supposedly saturated by the previous administration of 8 Gm. of ferrous sulfate twice daily for twelve days.

By means of experiments on their standardized anemic dogs Robscheit-Robbins and Whipple<sup>112</sup> have added corroborative evidence to the clinical observation that the rate of hemoglobin production bears a direct relation to the severity of iron deficiency anemia at the time of institution of specific therapy. In their experiments hemoglobin output rather than increase in the hemoglobin level of the blood was measured, and it was found that the maximum stimulus to the formation of hemoglobin occurred when the blood level was maintained at 6 Gm. per hundred cubic centimeters. When the standardized value was 11 Gm. the production of new hemoglobin amounted to two thirds of that obtained when the stimulus was maximal. These authors were able to demonstrate that in cases of simultaneous deficits of hemoglobin and of plasma protein, there was a tendency in anemic dogs toward the production of hemoglobin, regardless of the type of dietary protein supplied. They suggested that anoxemia and possibly other factors acted as stimuli to the formation of hemoglobin.

Hypochromic anemia was observed in rats by Vollmer and Melde<sup>113</sup> after prolonged feeding of cow's, sheep's or goat's milk. Anemia pro-

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110. Ross, J. F., and Chapin, M. A.: The Selective Absorption of Radioactive Iron by Normal and Iron Deficient Human Subjects, *J. Clin. Investigation* **20**: 437, 1941.

111. Erf, L. A.: Secretion of Orally Administered Radio-Iron in the Milk of Cows, *Proc. Soc. Exper. Biol. & Med.* **46**:284, 1941.

112. Robscheit-Robbins, F. S., and Whipple, G. H.: Hemoglobin Production Increases with Severity of Anemia, *Am. J. Physiol.* **134**:263, 1941.

113. Vollmer, H., and Melde, G. L.: Versuche über die Milchanämie der Ratte unter besonderer Berücksichtigung der Schafmilchanämie, *Klin. Wchnschr.* **20**:17, 1941.



duced by a diet of goat's or sheep's milk could be lessened or entirely corrected by the addition of carrots to the diet of the milk-producing animals. Sheep's milk anemia was successfully treated by feeding the rats a mixed diet, and its disappearance was hastened by the addition of carrot juice to their diet.

The effects produced in dogs by prolonged deficiency of vitamin B<sub>6</sub> have been studied by Street, Cowgill and Zimmermann.<sup>114</sup> Severe hypochromic anemia developed within one hundred and twenty to three hundred and twenty days. Rapid improvement followed the administration of vitamin B<sub>6</sub>, whereas ferrous sulfate was without effect on the anemia. Other abnormalities noted in the dogs suffering with a lack of vitamin B<sub>6</sub> were signs of cardiac insufficiency with hypertrophy of the right side of the heart and chronic passive congestion of the liver. Degenerative changes were observed in the myelin sheaths of the peripheral nerves and in the spinal cords of the experimental animals.

The role of cobalt in hemopoiesis continues to excite considerable interest, although as yet the fundamental question of whether cobalt is essential for the formation of hemoglobin by man or experimental animals has not been answered. The uncertainties of the problem are well expressed by Frost and his collaborators,<sup>115</sup> who conclude that their failure to obtain uniform results from cobalt may be due either to lack of specificity of its action or to the unavoidable cobalt content of their experimental diets, which may have satisfied the minimum requirements of their animals. These authors observed anemia in 2 puppies weaned and maintained on cow's milk and were able only partially to elevate the hemoglobin values by means of iron and copper. The addition of 0.1 mg. of cobalt to the daily diet of each of these 2 animals led to a further rapid increase. But in other controlled experiments involving dietary deficiency and hemorrhagic anemia no supplementary action of cobalt on hemoglobin formation could be demonstrated. Frost and his co-workers<sup>116</sup> also showed that in the case of dogs made anemic by hemorrhage the administration of cobalt prior to treatment with iron and copper appeared to prevent the expected therapeutic response to the latter substances. On the other hand, dried whole liver or liver extract effected rapid hemopoiesis in the cobalt-treated anemic animals. This result the authors attributed to some substance present in liver

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114. Street, H. R.; Cowgill, G. R., and Zimmermann, H. M.: Some Observations of Vitamin B<sub>6</sub> Deficiency in the Dog, *J. Nutrition* **21**:275, 1941.

115. Frost, D. V.; Elvehjem, C. A., and Hart, E. B.: Study of Need for Cobalt in Dogs on Milk Diets, *J. Nutrition* **21**:93, 1941.

116. Frost, D. V.; Spitzer, E. H.; Elvehjem, C. A., and Hart, E. B.: Some Effects of Cobalt and Liver Substance on Blood Building in Dogs, *Am. J. Physiol.* **134**:746, 1941.

other than iron, copper or vitamin B<sub>6</sub>. The same workers produced transient polycythemia in adult dogs by the addition of 3 to 6 mg. of cobalt per kilogram to the daily food ration. Cobalt fed to young dogs apparently possessed toxic properties and produced no changes in the blood. Copp and Greenberg<sup>117</sup> studied the metabolism of cobalt by means of its radioactive isotope. They found that cobalt was excreted chiefly in the urine and that after even minute doses, such as 10 micrograms, administered to a rat, most of the metal was quickly eliminated. In experiments of this type less than 5 per cent of the cobalt was found in the body after four days, indicating that the tissue requirements must be small.

Anemia developed in albino rats fed a diet containing deaminized casein, deficient in lysine, as the sole source of protein, according to Hogan and his associates.<sup>118</sup> If rats already anemic as the result of an exclusive milk diet are used in such experiments, the effects of lysine deficiency may be demonstrated more rapidly. The authors conclude that lysine is the antianemic factor present in casein and that it is the only essential amino acid the deficiency of which in deaminized casein is demonstrable by biologic experiments. As a preventive and corrective measure 130 mg. of lysine proved, in the authors' studies, slightly more efficacious than half this amount. They suggest that lysine may prove of importance in normal erythropoiesis.

A severe anemia of fish apparently due to nutritional deficiency has been described by Simmons and Norris.<sup>119</sup> It develops in spite of a high protein diet, with yeast as a source of the vitamin B complex. The anemia can be corrected by dietary supplements of whole liver, liver extract or fly maggots and by the injection of liver extract. Xanthopterin, either obtained from human urine or prepared synthetically, was found to be as efficacious as a refined and concentrated liver extract in curing the anemia of fingerling chinook salmon.

The injection into rabbits of small sublethal doses of tetanus toxin produces an anemia of hypochromic type, according to Farkas and Kligler.<sup>120</sup> When specific antitoxin was administered, reticulocytosis was observed, with a rapid return of the blood values to normal.

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117. Copp, D. H., and Greenberg, D. M.: Studies in Mineral Metabolism with the Aid of Artificial Radioactive Isotopes: Cobalt, *Proc. Nat. Acad. Sc.* **27**:153, 1941.

118. Hogan, A. G.; Powell, E. L., and Guerrant, R. E.: Anemia from Lysine Deficiency in Deaminized Casein, *J. Biol. Chem.* **137**:41, 1941.

119. Simmons R. W., and Norris, E. R.: Xanthopterin, the Fish Anemia Factor, *J. Biol. Chem.* **140**:679, 1941.

120. Farkas, H., and Kligler, I. J.: Production of Anemia by Tetanus Toxin, *Proc. Soc. Exper. Biol. & Med.* **48**:717, 1941.

The intake and excretion of iron by 4 healthy college girls were measured by Leverton.<sup>121</sup> The subjects were studied for three to eight months and received diets considered adequate except that the iron content was restricted to 3.5 to 4.5 mg. daily. The loss of iron exceeded the intake by 0.33 mg. daily when only 3 to 5 mg. was provided by the food. When a daily intake of 6.55 mg. was supplied, there was an average retention of 2.14 mg. The serum iron was decreased while the subjects were maintained on a low iron regimen and varied directly with the intake. To the author, these results suggest that no emphasis need be placed on amounts of iron exceeding 6.5 mg. daily in the diets of normal young women.

The site of absorption of iron from the gastrointestinal tract was investigated by Arrowsmith and Minnich.<sup>122</sup> Their data indicate that absorption occurs most readily in the stomach and duodenum, to a smaller degree in the jejunum and to an even lesser degree in the ileum. There was, however, no differentiation possible between absorption from the stomach and that from the duodenum.

The absorption of copper and the concentration of copper in the serum after oral ingestion of copper salts have been made the subject of study by Sachs and his co-workers.<sup>123</sup> The average basal level of copper in human serum was found to be 0.066 mg. per hundred cubic centimeters. The values obtained two hours after the ingestion of 2 to 16 mg. of copper sulfate ( $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ ) ranged between 0.090 and 0.110 mg. per hundred cubic centimeters. The authors conclude that copper is transported in the plasma in the same manner as iron. Experiments with isolated intestinal loops in dogs indicate that iron is absorbed chiefly in the upper and the middle jejunal loop and copper almost exclusively in the upper jejunal loop.

#### HEMOLYTIC AND ERYTHROBLASTIC ANEMIAS

*Acquired and Congenital Hemolytic Jaundice.*—Fundamentally important additions to the knowledge of the pathogenesis of anemias have in the past two years been limited to studies relative to factors

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121. Leverton, R. M.: Iron Metabolism in Human Subjects on Daily Intakes of Less than 5 Mg., *J. Nutrition* **21**:617, 1941.

122. Arrowsmith, W. R., and Minnich, V.: Site of Absorption of Iron from the Gastro-Intestinal Tract, *J. A. M. A.* **116**:2427 (May 24) 1941.

123. Sachs, A.; Levine, V. E.; Anderson, A. C., and Schmidt, A.: Studies on the Metabolism of Iron and Copper: Method for the Determination of Iron and Copper in Blood Serum, *J. Lab. & Clin. Med.* **26**:734, 1941; Rise in Serum Copper Following Oral Administration of Copper Sulphate, *Proc. Soc. Exper. Biol. & Med.* **46**:192, 1941. Sachs, A.; Levine, V., and Hughes, R.: Serum Copper and Iron, *Proc. Central Soc. Clin. Research* **14**:53, 1941.

responsible for the increased rate of destruction of circulating erythrocytes. Of greatest interest are the discoveries pertaining to the cause of erythroblastosis foetalis and certain hemolytic transfusion reactions and the demonstration that the spherical and fragile cell characteristic of familial hemolytic icterus does not, in all probability, represent an inborn error of erythrocyte formation but is the effect of extrinsic agents acting on the cell during its sojourn in the blood stream. Contributions in support of this concept were reviewed last year,<sup>123a</sup> and more recent substantiating evidence has been forthcoming.

The symptomatic and "acquired" types of hemolytic jaundice are discussed by a number of authors. Singer and Dameshek<sup>124</sup> point out that "neoplasms, both benign and malignant, are occasionally associated with a hemolytic spherocytic process." In addition, infectious and metabolic disorders may lead to an increased rate of erythrocyte destruction. The authors cite cases of dermoid cyst, pancreatic lymphosarcoma, Hodgkin's disease, lymphocytic leukemia, aleukemic leukemia, hepatic disease and lobar pneumonia, all accompanied by hemolytic anemia. In the case of pneumonia isohemolysins were demonstrated. In all cases the patients exhibited spherocytosis, and increased fragility was demonstrated in many instances. Various etiologic agents and mechanisms responsible for heightened red cell destruction are mentioned by the authors, including hemolysins, agglutinins, complement activity, mechanically induced trauma and damaged erythrocytes. In cases of the disorders reported the authors feel that splenectomy may be valueless, but that treatment of the underlying cause, such as removal of a dermoid cyst, is often curative.

A case of hemolytic jaundice considered to be of the acquired type is reported by Cook and Kotner.<sup>125</sup> In this case the patient was extremely ill and exhibited severe anemia, jaundice, an enlarged spleen, fever and reticulocytosis (92 per cent). Increased fragility of the erythrocytes was demonstrated. Cure was effected by splenectomy, and seven months after operation spherocytes were not found and results of the fragility test were normal. Fowler<sup>126</sup> believes that "undoubtedly most cases of primary hemolytic icterus are of the familial or congenital type." He

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123a. Goldhamer, S. M.; Sturgis, C. C., and Bethell, F. H.: Blood: Review of the Recent Literature, *Arch. Int. Med.* **67**:1177 (June) 1941.

124. Singer, K., and Dameshek, W.: Symptomatic Hemolytic Anemia, *Ann. Int. Med.* **15**:544, 1941.

125. Cook, J. E., and Kotner, L. M.: Acquired Hemolytic Jaundice: Report of a Case, *J. Missouri M. A.* **38**:354, 1941.

126. Fowler, W. M.: Acquired Hemolytic Icterus, *Ann. Int. Med.* **14**:1838, 1941.

reports 13 cases considered to represent instances of acquired hemolytic anemia. The group is heterogeneous, made up of cases of anemia for the most part obviously secondary to some other serious disorder, but in a few instances of apparent primary type. The author's data are scanty, but increased erythrocyte fragility was found in a number of instances. Fowler concludes that splenectomy may be of value in cases of primary acquired hemolytic jaundice and that the use of blood transfusions may induce dangerous reactions. He has frequently observed that the intensity of the jaundice failed to parallel the severity of the anemia.

Haden<sup>127</sup> classifies hemolytic anemias into two main groups, those characterized by intravascular destruction of erythrocytes and those dependent on increased removal of abnormal red cells by the spleen. In this classification disordered splenic function is disregarded but is mentioned subsequently as a remote possibility in occasional cases. According to the author, in all patients with evidence of increased red cell destruction certain special studies are indicated. These include estimation of spherocytosis by diameter and thickness measurements; tests for hemoglobinemia and hemoglobinuria; efforts at discovery of plasma hemolysins, which Haden says are not related to the spleen and are always absent in patients with congenital hemolytic jaundice; observation of autoagglutination of erythrocytes, usually apparent in counting chamber preparations, and abnormal weakness of erythrocyte stroma, as in sickle cell anemia and instances of in vitro spontaneous hemolysis. Haden reports 5 cases in which splenectomy was performed for one type or another of hemolytic anemia. In a patient with congenital hemolytic jaundice the operation was successful. A man aged 21 suffering from acute spherocytic hemolytic jaundice with increased erythrocyte fragility was not benefited by splenectomy and died. A patient with sickle cell anemia received partial relief after removal of the spleen. The condition of a girl aged 11 exhibiting paroxysmal nocturnal hemoglobinuria, or the Marchiafava-Micheli syndrome, was not improved by splenectomy, and her disorder was attributed by the author to defective erythrocyte stroma. A young woman aged 25 suffered with a familial form of hemolytic anemia characterized by in vitro spontaneous hemolysis, thought to be due to a stroma defect. Removal of the spleen was without effect on the hemolytic process.

Cases of classic congenital hemolytic jaundice illustrating various familial and clinical manifestations of the disorder have been reported by Dameshek,<sup>128</sup> Searls,<sup>129</sup> Branch,<sup>130</sup> Montgomery<sup>131</sup> and Hannay.<sup>132</sup>

127. Haden, R. L.: Splenectomy in Hemolytic Jaundice, *S. Clin. North America* **21**:1453, 1941.

128. Dameshek, W.: Familial Hemolytic Crisis: Report of Three Cases Occurring Within Ten Days, *New England J. Med.* **224**:52, 1941.

Instances of hemolytic anemia are occasionally encountered which are difficult to classify, since little is understood of their underlying mechanism. Such an occurrence, in an Italian woman aged 39 with "target cell" anemia, is reported by Eliel and Bayles.<sup>133</sup> The patient exhibited jaundice, reticulocytosis and splenomegaly, and as previously mentioned by Dameshek and Schwartz and by Wintrobe, the features of the disorder resembled those of Mediterranean anemia of children.

Paroxysmal nocturnal hemoglobinuria was encountered in a woman of 43 by Buell and Mettier.<sup>134</sup> The authors state:

After adding the patient's washed red blood cells to her serum and to normal serum a slight degree of hemolysis was observed. When the media were acidified with carbon dioxide, the hemolysis was greatly increased. When the serum was heated to 56° C., the hemolytic activity was destroyed. It seems apparent from these studies that the patient's red blood cells were sensitized to some lysin present in her own serum and in normal serum.

No complement fixation or Donath-Landsteiner reactions were observed in the blood of this patient. A study on a person with a similar type of intravascular hemolysis is reported by G. C. Ham and Horack.<sup>135</sup> The resistance of the erythrocytes to hypotonic solution of sodium chloride was normal. The authors were able to demonstrate by in vitro and in vivo tests that the hemolysis was associated with lowered  $p_H$  of the blood and consequently felt that the condition was representative of the Marchiafava-Micheli syndrome, although hemoglobinuria was noted only occasionally. They also demonstrated the thermolabile property of the plasma substance responsible for the hemolysis. Necropsy observations are given.

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129. Searls, H. H.: A Family with Hemolytic Icterus, *West. J. Surg.* **49**: 294, 1941.

130. Branch, C. D.: Congenital Hemolytic Jaundice (Spherocytic Jaundice), *Illinois M. J.* **80**:235, 1941.

131. Montgomery, L. C.: A Case of Familial Hemolytic Icterus, *Canad. M. A. J.* **45**:264, 1941.

132. Hannay, J. W.: Acholuric Familial Jaundice in the Third (Fourth?) Generation of Manifestation of the Disease, *Brit. J. Child. Dis.* **38**:65, 1941.

133. Eliel, L. P., and Bayles, T. B.: Microcytic Hypochromic Anemia Associated with Splenomegaly and Refractory to Treatment: Report of Case, *New England J. Med.* **225**:134, 1941.

134. Buell, A., and Mettier, S. R.: Paroxysmal Nocturnal Hemoglobinuria with Hemolytic Anemia (Marchiafava-Micheli Syndrome), *J. Lab. & Clin. Med.* **26**:1434, 1941.

135. Ham, G. C., and Horack, H. M.: Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinemia: Report of a Case with Only Occasional Hemoglobinuria and with Complete Autopsy, *Arch. Int. Med.* **67**:735 (April) 1941.

March hemoglobinuria was made the subject of an extensive article by Gilligan and Blumgart,<sup>136</sup> in which the literature bearing on this poorly understood condition is reviewed and 3 cases, which were investigated in detail, are reported. In all of the cases the patients were young men in whom hemoglobinuria developed after various degrees of exercise. Two of the subjects exhibited slight jaundice, and in 1 the spleen and the liver were palpable. In all of the patients erythrocyte, leukocyte, platelet and reticulocyte counts were normal, and the fragility of the red cells as tested both by hypotonic solution of sodium chloride and by trauma was identical with that of cells from control subjects. No auto-agglutination in the cold was demonstrated in these cases. Hemoglobin was excreted for one to three hours during an attack, but the amount of hemoglobin contained in the urine was always less than 10 per cent of the calculated free hemoglobin in the plasma. In this disease jaundice and enlargement of the liver and the spleen are rare. The pigment present in the urine is oxyhemoglobin. There is no evidence of impaired renal function as measured by the urea clearance test. Exercise and a lordotic posture are requisites for the occurrence of hemoglobinuria, but the mechanism of intravascular hemolysis is unknown. The condition is benign.

A case of hemoglobinuria of obscure origin is reported by Altschule and Gilligan.<sup>137</sup> Their patient was a 77 year old Russian Jew whose erythrocyte level fell from 4,700,000 to 2,900,000 per cubic millimeter and whose hemoglobin concentration decreased from 94 to 59 per cent during a period of approximately three weeks. Hemoglobinuria and hemoglobinemia were most marked during the early part of the attack. The liver and the spleen were enlarged, and the renal function was impaired. By calculation based on the urobilin content of the feces and the plasma hemoglobin values, the authors arrived at the conclusion that all of the hemoglobin obtained from red cell destruction during the course of the attack was released into the circulation. This phenomenon is in contrast to that observed in the more common types of hemolytic crisis, in which, in spite of the rapid development of severe anemia, there is no evidence of intravascular hemolysis. No abnormalities of the erythrocytes were found in this patient, and spontaneous recovery was complete.

136. Gilligan, D. R., and Blumgart, H. L.: March Hemoglobinuria: Studies of the Clinical Characteristics, Blood Metabolism and Mechanism, with Observations on Three New Cases, and Review of the Literature, *Medicine* **20**:341, 1941.

137. Altschule, M. D., and Gilligan, D. R.: Acute, Massive Hemoglobinuria of Obscure Cause, with Jaundice and Anemia: Report of Case with Clinical and Hematologic Studies and Measurements of Blood Pigment Metabolism, *Arch. Int. Med.* **68**:957 (Nov.) 1941.

Just before his death Lederer<sup>138</sup> described a type of sporadic acute hemolytic anemia, occurring in Baghdad, Iraq, and characterized by abrupt onset, abdominal pain, vomiting, pallor, faintness, rapidly developing anemia and a high degree of leukocytosis. Normal erythrocyte fragility was uniformly present. Of 13 cases encountered, the disease was fatal in 1. Transfusions and intramuscular injections of blood, parenteral administration of liver extract and the use of epinephrine were found of value in the therapy of this condition. Lederer considered that the disorder was similar to favism, and he suspected that it was due to a sensitization reaction brought about by contact with flowers blooming in the parks of Baghdad. The disease has been observed only in the spring and occurs chiefly in children of a fairly definite constitutional type.

An acute hemolytic crisis occurring in a man aged 54 was observed by Hargraves and his associates.<sup>139</sup> The attack occurred one week after an uneventful operation for a ureteral stone. The interesting feature of the case was the evidence of active erythrophagocytosis by monocytes, macrophages and neutrophils. There was rapid development of anemia, reticulocytosis, hyperbilirubinemia and a high degree of leukocytosis. Within twenty-four hours after transfusion of blood signs of red cell destruction disappeared, and recovery was subsequently complete.

A comparative study of the blood on normal subjects and on persons who had undergone splenectomy for relief of various conditions is reported by Singer and his co-workers.<sup>140</sup> Common changes induced by splenectomy include the presence of Howell-Jolly bodies and "target cell" erythrocytes, increased resistance of the red cells to hypotonic solution of sodium chloride, lowered "hemolytic index," increased "lysolecithin" metabolism, leukocytosis and thrombocytosis. To the authors their observations indicate that the spleen exerts direct effects on the erythrocytes which traverse its sinusoids and indirect effects on the hemopoietic cells of the bone marrow.

A study of the significance of "target cells" was undertaken by Bohrod.<sup>141</sup> He observed such cells commonly during periods of regeneration after hemorrhage or hemolysis, regardless of the cause. The

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138. Lederer, R.: New Form of Acute Haemolytic Anaemia, "Baghdad Spring Anaemia," *Tr. Roy. Soc. Trop. Med. & Hyg.* **34**:387, 1941.

139. Hargraves, M. M.; Herrell, W. E., and Pearman, R. O.: Erythrophagocytic Anemia (Lederer's Anemia?): Report of a Case with Recovery, *Proc. Staff Meet., Mayo Clin.* **16**:107, 1941.

140. Singer, K.; Miller, E. B., and Dameshek, W.: Hematologic Changes Following Splenectomy in Man, with Particular Reference to Target Cells, Hemolytic Index and Lysolecithin, *Am. J. M. Sc.* **202**:171, 1941.

141. Bohrod, M. G.: The Significance of Target Cells in Anemia, *Am. J. M. Sc.* **202**:869, 1941.



author demonstrated increased resistance of target cells to hypotonic solution of sodium chloride and to 2 per cent acetic acid. He believes that this type of erythrocyte is produced by the bone marrow in response to the stimulus of blood destruction and that the contention that the target cell represents a fundamental defect characteristic of any specific anemia is unjustified.

Singer<sup>142</sup> describes a method for the expression of the lysolecithin content of serum as measured by its hemolytic effect on normal red cells. He finds no evidence of increased lysolecithin content of the serum in cases of hemolytic jaundice, and he believes that lysolecithin is probably not active in the normal destruction of erythrocytes.

T. H. Ham and Castle<sup>143</sup> point out that the spleen in serving as a reservoir for red cells induces erythrostasis. With loss of plasma erythroconcentration occurs. An analogous condition was produced in vitro, with the observation of spherocytosis and increased fragility. Erythrostasis was induced in dogs by ligation of the splenic veins and by soluble pentobarbital anesthesia. The authors suggest that their observations may throw light on the mechanism responsible for the crisis of congenital hemolytic jaundice and sickle cell anemia. It is thought that infections may act by increasing the plasma content of globulin, with consequently greater blood viscosity leading to erythrostasis, erythroconcentration and increased susceptibility to hemolysis. In sickle cell anemia a vicious cycle may be inaugurated by decreased oxygen tension, which leads to abnormalities of red cell shape with a consequent delay in passage through the capillaries that in turn entails still further losses in oxygen content, with aggravated sickling, erythrostasis and greatly augmented hemolysis.

By the use of red cells "tagged" with radioactive iron Cruz and his associates<sup>144</sup> showed that the new cells in the circulation are markedly less resistant than older cells to the hemolytic action of hypotonic solutions of sodium chloride. This difference in susceptibility to hemolysis disappeared after three to four days. Their observations also indicate that old erythrocytes, which have been in the circulation for one hundred

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142. Singer, K.: Lysolecithin and Hemolytic Anemia: The Significance of Lysolecithin Production in the Differentiation of Circulating and Stagnant Blood, *J. Clin. Investigation* **20**:153, 1941.

143. Ham, T. H., and Castle, W. B.: Relation of Increased Hypotonic Fragility and of Erythrostasis to the Mechanism of Hemolysis in Certain Anemias, *Proc. Phil. Soc.* **82**:411, 1940; *Tr. A. Am. Physicians* **55**:127, 1940.

144. Cruz, W. O.; Hahn, P. F.; Bale, W. F., and Balfour, W. M.: Effect of Age on Susceptibility of Erythrocyte to Hypotonic Salt Solutions: Radioactive Iron as Means of Tagging Red Blood Cell, *Am. J. M. Sc.* **202**:157, 1941.

and thirty days, are more resistant to hypotonic solution of sodium chloride than the red cells of the mean age group.

On the basis of studies of the lytic action of saponin on rabbit erythrocytes Ponder and his co-workers<sup>145</sup> state that the lytic activity of a simple lysin in vivo compared to that in the usual in vitro test system involves three factors: the effect of the high concentration of cells and the presence of serum inhibition in vivo, the fact that lysins are taken up by the tissues in vivo and the fact that the lysins may be constantly supplied in vivo. Taking these factors together, the lytic activity of a lysin in the whole animal is probably only about one two-hundredth that observed in the usual in vitro test systems. Heilman and Herrell<sup>146</sup> have shown that gramicidin has a powerful hemolytic action against rabbit's and sheep's erythrocytes in vitro.

Gilligan and his associates<sup>147</sup> injected stroma-free human hemoglobin into the blood stream of 10 normal persons, 3 patients with albuminuria due to congestive heart failure and 1 patient with carcinoma of the colon. Various toxic reactions were observed after the larger doses. Hemoglobin was excreted in the urine by all normal subjects when the plasma hemoglobin content was raised above 135 mg. per hundred cubic centimeters. The plasma bilirubin level was elevated after the intravenous injection of hemoglobin.

*Hemolytic Anemia Produced by Sulfanilamide and Its Derivatives.*—Eight cases of hemolytic anemia with 2 deaths following the administration of sulfanilamide and 1 case with recovery occurring during treatment with sulfapyridine (2-[paraaminobenzenesulfonamide]-pyridine), are reported by Craddock.<sup>148</sup> In 3 cases in which treatment was with sulfanilamide moderate to marked nitrogen retention developed, without signs of clinical uremia. The renal lesions in the fatal cases were similar to those observed after transfusion reactions. In the presence of acute hemolytic anemia associated with therapy with a sulfanilamide compound the author believes that the urine should be alkalinized as rapidly as possible. Nine cases of acute hemolytic anemia with 6 deaths during treatment with sulfanilamide or one of its derivatives were encountered

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145. Ponder, E.; Hyman, C., and White, L.: The Activity of Hemolysins in Vivo, *Am. J. Physiol.* **132**:18, 1941.

146. Heilman, D., and Herrell, W. E.: Hemolytic Effect of Gramicidin, *Proc. Soc. Exper. Biol. & Med.* **46**:182, 1941.

147. Gilligan, D. R.; Altschule, M. D., and Katersky, E. M.: Studies of Hemoglobinemia and Hemoglobinuria Produced in Man by Intravenous Injection of Hemoglobin Solutions, *J. Clin. Investigation* **20**:177, 1941.

148. Craddock, G. B.: Acute Hemolytic Anemia and Renal Insufficiency of Sulfanilamide and Sulfapyridine Therapy, *Virginia M. Monthly* **68**:353, 1941.

during one year by Fox and Ottenberg.<sup>149</sup> In 4 cases, including 2 which terminated fatally, detailed laboratory studies were carried out. Pigment analyses were made of erythrocytes which survived hemolysis, serum and urine. The surviving red cells were essentially normal, containing little methemoglobin or sulfhemoglobin. Samples of serum secured twelve to forty-eight hours after the onset of hemolysis contained 0.4 to 1.7 Gm. per hundred cubic centimeters of three blood pigments: hemoglobin, methemoglobin and Fairley's methemalbumin. Sulfhemoglobin was not found. Calculations of the weights of hemoglobin liberated, the amounts in the serum after twelve to forty-eight hours and the quantities excreted in the urine showed that the body has means of removing rapidly from the plasma 500 to 700 Gm. of hemoglobin without the aid of renal excretion. Shock was a conspicuous feature in these cases. The hemolyzed cells represented about 30 per cent of the total blood volume, and this is thought to be a possible explanation of the hemolytic shock. Death did not appear to be due to the toxicity of the free hemoglobin or to uremia from blockage of renal tubules. Transfusions of blood were not of much therapeutic value in these cases because of hemolysis of the transfused cells. The author suggests that plasma infusions may be preferable to transfusions of whole blood in the management of patients with acute hemolytic anemia. Additional cases of hemolytic anemia following the use of sulfanilamide or one of its derivatives are reported by Myers and Rom,<sup>150</sup> Quick and Lord,<sup>151</sup> Trier<sup>152</sup> and Aulia.<sup>153</sup>

Hemolytic anemia was induced in rats during sulfanilamide administration by Antopol and his co-workers.<sup>154</sup> After the drug had been given for two weeks in a dose of 1 Gm. per kilogram daily the erythrocytes showed a significantly increased resistance to hypotonic solution of sodium chloride.

*Erythroblastosis Foetalis and Icterus Gravis Neonatorum.*—Probably the outstanding contribution of the past year to hematologic knowledge and to pediatric practice concerns the elucidation of the etiologic mecha-

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149. Fox, C. L., Jr., and Ottenberg, R.: Acute Hemolytic Anemia from the Sulfonamides, *J. Clin. Investigation* **20**:593, 1941.

150. Myers, G. B., and Rom, J.: Acute Hemolytic Anemia, Hemoglobinuria and Uremia Following Sulfanilamide, *Ann. Int. Med.* **14**:164, 1940.

151. Quick, E. D., and Lord, F. D.: Acute Hemolytic Anemia Following Sulfathiazole Administration: Report of Case with Recovery, *J. A. M. A.* **117**:1704 (Nov. 15) 1941.

152. Trier, M.: Acute Hemolytic Anemia Caused by Treatment with Substances of the Sulfanilamide Group, *Ugesk. f. læger* **103**:814, 1941.

153. Aulia: Acute Hemolytic Anemia Caused by Prontosil, *Geneesk. tijdschr. v. Nederl.-Indië* **81**:2167, 1941.

154. Antopol, W.; Goldman, L., and Sampson, W. J.: Erythrocyte Fragility Changes Produced by Sulfanilamide, *Am. J. M. Sc.* **202**:163, 1941.

nism of erythroblastosis foetalis by Levine, Burnham and their collaborators.<sup>155</sup> Their work represents an application of the discovery by Landsteiner and Wiener that about 85 per cent of human beings have the rhesus agglutinin in their erythrocytes, whereas approximately 15 per cent do not. Of 153 cases of erythroblastosis foetalis, 93 per cent were shown to be due to isoimmunization of a mother without the rhesus agglutinin in her blood by the rhesus factor in the red cells of the fetus. The maternal agglutinins thus formed are able to pass through the placental barrier into the fetal circulation and there produce massive agglutination and destruction of the fetal corpuscles. In such cases, antirhesus agglutinins were found in the blood of about 50 per cent of mothers without the rhesus agglutinin for as long as two months after delivery. The reaction is considered a possible cause of spontaneous abortions. The blood of 4 of 5 mothers who had infants exhibiting erythroblastosis foetalis or hydrops foetalis or who had been delivered of stillborn macerated fetuses was shown to lack the rhesus agglutinin. In 4 of the mothers reactions occurred after blood transfusions, 2 of which resulted in the deaths of the mothers. The blood of the donors, the husbands and the infants was found to contain the rhesus factor. In such circumstances it is believed that the donor's cells are destroyed by the recipient's immune bodies formed in response to the presence of the fetal rhesus agglutinin. If the presence of the antirhesus agglutinin is suspected, the authors recommend a modified cross-matching technic to be employed before transfusions are given during the course of or for some months after the termination of pregnancy. The mixed serum and cell suspensions should be incubated at 37 C. for thirty minutes before centrifuging, in accordance with the Landsteiner technic. It is suggested that blood examinations should be made soon after birth in the case of babies suspected of potential erythroblastosis foetalis, in order that life-saving transfusions may be instituted as early as possible.

Unlike the A and B blood factors, the rhesus factor could not be demonstrated in the saliva, sperm cells or seminal fluid of persons with the agglutinin in the blood. Levine and Katzin conclude that it may with justification be assumed that the rhesus agglutinin is limited to the erythrocytes.

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155. Levine, P.; Burnham, L.; Katzin, E. M., and Vogel, P.: The Role of Iso-Immunization in the Pathogenesis of Erythroblastosis Fetalis, *Am. J. Obst. & Gynec.* **42**:925, 1941. Levine, P.: The Role of Iso-Immunization in Transfusion Accidents and in the Pathogenesis of Erythroblastosis Fetalis, *Am. J. Clin. Path.* **11**:898, 1941. Burnham, L.: Common Etiology of Erythroblastosis and Transfusion Accidents in Pregnancy, *Am. J. Obst. & Gynec.* **42**:389, 1941. Levine, P., and Katzin, E. M.: Pathogenesis of Erythroblastosis Foetalis: Absence of the Rh Factor from Saliva, *Proc. Soc. Exper. Biol. & Med.* **48**:126, 1941.

Fifteen instances of erythroblastosis foetalis occurred among 22,209 infants delivered at the St. Louis Maternity Hospital, according to Wachter.<sup>156</sup> In 20 of 22 cases reported by the author the infants were jaundiced at birth. The proportion of males to females was 13 to 9. The average age of the mothers was 30 years, and their average parity was 4. Only 1 of the infants in this series was born of a primigravida. Repetition of one or more of the different types of fetal erythroblastosis occurred in 46 per cent of the families represented in this survey. The mortality of the affected infants was 42 per cent. Danis<sup>157</sup> discusses the importance of isoimmunization to the rhesus factor in the causation of erythroblastosis foetalis and emphasizes the subsidiary effects of hepatic dysfunction on the course of the disease. Esch<sup>158</sup> regards the anemia as primarily of hemolytic origin but also finds disturbed hepatic function responsible for the later manifestations of the disorder.

Two infants with severe icterus gravis were observed at the ages of 6½ and 17 months, respectively, by Sobel.<sup>159</sup> Avoidance of fatal outcome was attributed to blood transfusion therapy. Neither of the patients exhibited stigmas of kernicterus. According to the author, the tetralogy of kernicterus consists of opisthotonos, choreoathetosis, extrapyramidal spasticity and mental deficiency.

The incidence of erythroblastosis foetalis is greater than is generally recognized, according to Platore.<sup>160</sup> He regards the disorder as an important cause of infant mortality, accounting for about 5 per cent of neonatal deaths. Most observers have found blood transfusions of specific value in the treatment of this disorder, but Moore<sup>161</sup> reports a case with refractoriness to transfusion, but with recovery following the parenteral injection of liver extract. Success has attended therapy with vitamin K and bile salts, according to Mayman.<sup>162</sup> In 8 of 9 fatal cases of icterus gravis with erythroblastosis observed by Rinehart and Smyth<sup>163</sup>

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156. Wachter, H. E.: Erythroblastosis Foetalis, *Weekly Bull. St. Louis M. Soc.* **36**:51, 1941.

157. Danis, P. G.: Recent Observations on the Etiology, Course, and Treatment in Icterus and Anemia of the Newborn, *Weekly Bull. St. Louis M. Soc.* **36**:46, 1941.

158. Esch, P.: Zur Genese des Icterus neonatorum, *Zentralbl. f. Gynäk.* **65**:574, 1941.

159. Sobel, I. P.: Favorable End Results in Icterus Gravis Neonatorum, *J. Pediat.* **18**:621, 1941.

160. Platore, R. V.: Erythroblastosis Foetalis, *Journal-Lancet* **61**:151, 1941.

161. Moore, J. C.: Blood Dyscrasias in Newborn, *Nebraska M. J.* **26**:282, 1941.

162. Mayman, E. W.: Erythroblastosis in Icterus Gravis Neonatorum Successfully Treated with Vitamin K, *J. Pediat.* **17**:806, 1940.

163. Rinehart, J. F., and Smyth, F. S.: Changes in the Adrenal Glands in Cases of Icterus Gravis with Erythroblastosis, *Am. J. Dis. Child.* **62**:896 (Oct.) 1941.

changes were found in the fetal portion of the adrenal cortex. The authors suggest that an unrecognized endocrine abnormality of the maternal organism may possess etiologic significance. Cases of erythroblastosis foetalis and icterus gravis are described by Bertrand and Guilbault,<sup>164</sup> Vinnecour,<sup>165</sup> Lyman,<sup>166</sup> Ruiz<sup>167</sup> and Stodtmeister.<sup>168</sup>

*Sickle Cell Anemia.*—Two hundred and seventy-five Negro patients were examined by Tomlinson.<sup>169</sup> Eighteen instances of sickle cell anemia were detected by the method of Hansen-Prüss, an incidence of 6.5 per cent. None of the patients had frank anemia. A woman with anemia from bleeding uterine fibromyomas died during the course of operation. She was given three transfusions of blood without untoward effects, but the fourth was followed by a severe febrile reaction. Sickle cells were observed in the vascular system of the tissues removed at operation, but necropsy was not performed. Subsequently, the sickling trait was demonstrated in the blood of the last-used donor. The author points out the possible danger of accidental use in transfusion of blood from a donor with sickle cell anemia and the risk of inducing sickle cell anemia by surgical procedures on patients exhibiting the sickling trait.

The complication of pregnancy in patients with sickle cell anemia is discussed by Koback and his associates.<sup>170</sup> A total of 17 cases has been reported in the literature, including 6 observed by the authors. Five deaths occurred in the complete series, but this figure probably bears little relation to the actual mortality, since the incidence of pregnancy complicating sickle cell anemia is undoubtedly much higher than is indicated by the small number of reported cases, and the fatal instances are more likely to be commented on in the literature. The authors describe women with sickle cell anemia as being usually thin and underdeveloped, suffering frequent attacks of joint, muscle and vague abdominal pains with nausea and vomiting and being unusually sus-

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164. Bertrand, A., and Guilbault, A.: Un cas d'érythroblastose du nouveau-né avec ictère, *Union méd. du Canada* **70**:1301, 1941.

165. Vinnecour, M. I.: Icterus Gravis Neonatorum, *Am. J. Dis. Child.* **62**: 681 (Sept.) 1941.

166. Lyman, G. D.: Anemia of Newborn with Erythroblastosis, *California & West. Med.* **54**:64, 1941.

167. Ruiz, C.: Anemia idiopática del recién nacido, *Día méd.* **13**:184, 1941.

168. Stodtmeister, R.: Akute Erythroblastose und erythroblastische Reaktion, *Klin. Wchnschr.* **20**:444, 1941.

169. Tomlinson, W. J.: Studies of Sickle Cell Blood, with a New Method for Its Rapid Diagnosis, *Am. J. Clin. Path.* **11**:835, 1941.

170. Koback, A. J.; Stein, P. J., and Daro, A. F.: Sickle Cell Anemia in Pregnancy: A Review of the Literature and Report of Six Cases, *Am. J. Obst. & Gynec.* **41**:811, 1941.

ceptible to infections of the respiratory tract. Jaundice and ulcers of the legs are common, and cardiorespiratory symptoms are frequently associated with severe anemia. During gestation hypertensive or pre-eclamptic toxemia is often observed. Puerperal septic morbidity is frequent. Pregnancy apparently has an unfavorable effect on a woman with sickle cell anemia. The prognosis for the fetus is poor. Abortions and stillborn macerated infants are common. Repeated use of blood transfusions is beneficial in carrying pregnancy to successful completion in the presence of sickle cell anemia.

The case of a 12 year old girl suffering with sickle cell anemia who experienced sudden hemiplegia and recovered is reported by Younge and McIntosh.<sup>171</sup> A Negro boy aged 12 with both sickle cell anemia and acute rheumatic disease was observed by Walker and Murphy.<sup>172</sup> After many transfusions had been given, a cerebral hemorrhage developed and the patient died. Necropsy failed to reveal the source of the hemorrhage. There was no evidence of generalized vascular disease or of thrombosis, but focal areas of ganglion cell loss were present in the gray matter. A possible connection between the large number of transfusions and the occurrence of the cerebral hemorrhage is mentioned by the authors.

Two fatal cases of sickle cell anemia are reported by Vance and Fisher.<sup>173</sup> In 1 case the patient was a boy of Greek parentage, who died at the age of 6 years. The other fatality occurred in a Negress aged 49, and death was attributed to fat embolism in the lungs, kidneys, myocardium and brain. The source of the fat was believed to be the bone marrow.

Unusual bone changes in the metacarpals and phalanges of a Negro infant with sickle cell anemia were observed by Danford, Marr and Elsey.<sup>174</sup> The changes were abrupt in onset and consisted of irregular areas of decreased density involving the medial cavity, the cortex and the periosteum. There was thickening of the periosteum along the shafts of the bones. The lesions resembled those caused by syphilis or tuberculosis, but during a period of four months they gradually and completely disappeared. Hyperkeratotic plaques, not considered typical

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171. Younge, W. A., and McIntosh, E. F., Jr.: Case Report: Sickle Cell Anemia with Hemiplegia, *J. Nat. M. A.* **33**:130, 1941.

172. Walker, D. W., and Murphy, J. P.: Sickle Cell Anemia Complicated by Acute Rheumatic Heart Disease and Massive Cerebral Hemorrhage: Case Report, *J. Pediat.* **19**:28, 1941.

173. Vance, B. M., and Fisher, R. C.: Sickle Cell Disease: Two Cases, One Presenting Fat Embolism as Fatal Complication, *Arch. Path.* **32**:378 (Sept.) 1941.

174. Danford, E. A.; Marr, R., and Elsey, E. C.: Sickle Cell Anemia, with Unusual Bone Changes, *Am. J. Roentgenol.* **45**:223, 1941.

of any known disease, were observed by Smith and Lewe<sup>175</sup> on both thighs and the left leg and ankle of a 39 year old Negro with sickle cell anemia. A case of sickle cell anemia with ulcer of the ankle in a Negress aged 39 is reported by Ebert.<sup>176</sup> A patient with sickle cell anemia received arsenical therapy for secondary syphilis without manifesting signs of intolerance to the drug employed, according to Tiant and Morales Coello.<sup>177</sup> Four patients with sickle cell anemia were treated by Vryonis<sup>178</sup> by the intravenous injection of 20 cc. of liver extract. In 1 case a favorable hematologic response was obtained, which the author attributes to the liver therapy employed.

*Erythroblastic (Cooley's) Anemia.*—A series of 15 cases of Cooley's anemia is reported by Pierce.<sup>179</sup> There was no favorable response to any form of treatment employed. The author submits evidence that adults who are potential transmitters of the disease may be detected by the performance of erythrocyte fragility tests and the discovery of abnormally resistant red cells.

Several articles dealing with erythroblastic anemia have been published by Acuña,<sup>180</sup> one with an associate. He reports 11 instances of the disease and discusses possible etiologic factors and the effects of therapy, particularly splenectomy. The presence of syphilis, tuberculosis, malaria or leishmaniasis in the parents of the affected children was excluded. The ancestors of the patients had been inhabitants of the Mediterranean area. Abnormalities in form and size of the erythrocytes were observed in the mothers of 2 of the patients. The author believes that the disease is caused by an inherited absence of some factor necessary for the normal development of the erythrocyte. Splenectomy was performed on 2 children, with apparent temporary improvement,

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175. Smith, E. M., Jr., and Lewe, I. A.: Sickle Cell Anemia Associated with Chronic Ulcers of the Leg and Hyperkeratotic Plaques, *Arch. Dermat. & Syph.* **44**:946 (Nov.) 1941.

176. Ebert, M. H.: Sickle Cell Anemia with Ulcer of the Left Ankle, *Arch. Dermat. & Syph.* **44**:948 (Nov.) 1941.

177. Tiant, F. R., and Morales Coello, J. R.: Un caso de drepanocitemia asociado a sífilis secundaria reciente, con tolerancia perfecta al tratamiento específico, *Vida nueva* **48**:244, 1941.

178. Vryonis, G.: Studies of Effect of Intravenous Administration of Liver Extract in Patients with Sickle Cell Anemia: An Unusual Response, *J. Lab. & Clin. Med.* **26**:1470, 1941.

179. Pierce, M. I.: Erythroblastic Anemia: A Clinical Study, *Proc. Inst. Med. Chicago* **13**:336, 1941.

180. Acuña, M.: Nuevas observaciones de anemia de von Jaksch-Luzet-Cooley: Anemia eritroblástica tipo Cooley, *Arch. argent. de pediat.* **16**:286, 1941; Anemia de von Jaksch-Luzet-Cooley, *Prensa méd. argent.* **28**:2069, 1941. Acuña, M., and Bonduel, A.: Estudio de la función hepática en las anemias eritroblásticas, *Arch. argent. de pediat.* **15**:413, 1941.



but ultimately both died of the anemia. Transfusions were found of value in reducing the susceptibility to infection. Acuña believes that the course of erythroblastic anemia is adversely affected by progressive hepatic damage. He has demonstrated the deposition of pigment at the periphery of the liver lobules and finds evidence of injury to the cells of the interlobular zones caused by persistent jaundice. Abnormalities of hepatic function were revealed by the galactose tolerance and the hippuric acid excretion test and by the observation of a direct van den Bergh reaction in 3 cases.

The case of a youth of 19 years with all the features of Cooley's anemia is reported by Smith,<sup>181</sup> who first observed him at the age of 4. A brother aged 8 suffers from the same disorder. Both parents and a brother of these patients exhibit basophilic stippling of the circulating erythrocytes and increased red cell resistance to hypotonic solution of sodium chloride. The author believes that these nonanemic relatives with abnormal red cells are carriers of Cooley's anemia.

Three patients with Cooley's anemia were treated by Goldman and Malavazos<sup>182</sup> with chorionic gonadotropin and vitamin B<sub>6</sub>. Administration of the former agent was accompanied by elevation of the red cell level and erythroid hyperplasia of the bone marrow. The subsequent use of vitamin B<sub>6</sub> appeared to be of some value in maintaining the improved status of the peripheral blood. A typical instance of Cooley's anemia with roentgen observations is reported by Wood.<sup>183</sup>

#### APLASTIC AND REFRACTORY ANEMIAS

Bomford and Rhoads<sup>184</sup> have emphasized that the efficient use of liver and iron as therapeutic agents has brought into prominence a group of patients with severe anemia whose course of illness cannot be significantly altered by any known treatment. This therapeutically resistant characteristic they employ as the sole criterion of the group of anemias for which they propose a new classification based on the changes in the bone marrow. They include, in addition to a considerable number of other types, the syndromes of aplastic anemia, pseudoaplastic anemia,

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181. Smith, C. H.: Cooley's Anemia: Familial Aspects of a Case in Which the Patient Was Observed from Early Childhood to Young Adult Life, *Am. J. Dis. Child.* **62**:1115 (Nov.) 1941.

182. Goldman, L. M., and Malavazos, A.: Effect of Pregnancy-Urine Hormone and Vitamin B<sub>6</sub> on the Blood and Bone Marrow Pictures in Primary Erythroblastic Anemia, Cooley, *J. Clin. Endocrinol.* **1**:945, 1941.

183. Wood, B. J.: Erythroblastic Anemia: Report of Case, *Proc. Staff Meet., Mayo Clin.* **16**:202, 1941.

184. Bomford, R. R., and Rhoads, C. P.: Refractory Anaemia: I. Clinical and Pathological Aspects, *Quart. J. Med.* **10**:175, 1941.

achrestic anemia, *l'anémie maligne intermédiaire* and leukocytopenic leukemia. Excluded from this group are anemias secondary to cancer, tuberculosis, lymphogranuloma, nephritis, cirrhosis of the liver, sepsis, infective endocarditis and frank leukemia. Their classification of 58 cases of anemia which proved resistant to all forms of treatment except blood transfusions comprises the four following groups, based on the histologic appearance of bone marrow obtained either by sternal aspiration during life or at necropsy:

1. Pseudoaplastic anemia, characterized by a partly mature cellular marrow. In this group, the marrow differed the least from normal, symptoms were relatively mild, the illness was sometimes of long duration and spontaneous remissions were not uncommon. Leukocytopenia and thrombopenia were inconspicuous or absent, and hemorrhages and infections occurred infrequently. Pigmentation of the skin was occasionally noted and, less frequently, hemochromatosis. In some cases this type of anemia appeared to be a temporary phase in the development of other disorders of the hemopoietic system.

2. Aplastic anemia with a hypoplastic marrow. In this group, as compared with group 1, the duration was shorter, such symptoms as hemorrhage were more severe and spontaneous remissions occurred less frequently. Leukocytopenia and thrombopenia were present in all cases.

3. Chronic granulocytopenia with immature cellular marrow. The average duration of the illness was short, and the most prominent clinical feature was the occurrence of areas of necrosis and infection, particularly in the neighborhood of the mouth and the anus.

4. Myelosclerosis with fibrosis, sclerosis and giant cell hyperplasia. The illness was of relatively brief duration and the outcome uniformly fatal. The most prominent clinical feature was a progressive and considerable enlargement of the spleen and the liver. It is emphasized that the onset of a remission in a refractory anemia is usually heralded by an increase in the white cell count, the color index and the mean corpuscular volume. Remissions may be partial or complete. When they are incomplete, the blood picture may resemble closely that seen in the mild macrocytic anemia of hepatic disease.

A second most comprehensive and valuable article is presented by Bomford and Rhoads<sup>185</sup> on the etiology and treatment of refractory anemia. According to them, race, sex, age and family history do not appear to have any influence on the occurrence of the disease. In their group of patients, such anemia rarely occurred before 20 or after 60 years of age. Their observations suggest that there might be some

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185. Bomford, R. R., and Rhoads, C. P.: Refractory Anaemia: II. Etiology and Treatment, *Quart. J. Med.* **10**:235, 1941.

association with this type of anemia and eunuchoidism, menstruation and the menopause. It is of interest to note that achlorhydria apparently does not play a role in the causation of this disease. Of great importance from an etiologic standpoint is the evidence that 24 of the 66 patients studied were exposed to a potentially toxic substance, such as benzene, hair dye (paraphenylenediamine type), arsphenamine, radioactive paint, roentgen rays and radium and various drugs. Hepatic function tests indicated hepatic impairment in 3 patients, and in addition, in 14 of 26 patients one or another of the three hepatic function tests employed gave abnormal results. The authors regard damage to this organ as an important factor in the causation of refractory anemia and one which merits further investigation. Careful studies indicate that the disturbance of pigment metabolism in this condition is similar to that encountered in diseases of the liver and unlike that observed in pernicious anemia and in hemolytic jaundice. The rate of excretion of bilirubin in the feces is increased above normal in some cases in all four types of refractory anemia and in one half of the patients examined. The red cells in patients with refractory anemia were found to be slightly more resistant to lysis by saponin than normal cells. The hemolytic substances encountered in the urine of normal persons occur in bound or conjugated form in the urine of patients with refractory anemia. A study of the excretion of glucuronates and sulfates after a test dose of aminopyrine suggests the existence of an abnormality in the process of detoxication in patients with refractory anemia. As a working hypothesis of the causation of this variety of anemia, it is suggested that it may be due to a conditioned susceptibility to toxic substances, usually exogenous or endogenous aromatic hydrocarbons, associated with hepatic dysfunction, a failure of biochemical mechanisms of detoxication and the circulation of hemolytic substances. It is considered possible that these hemolysins cause either an abnormal form of hemolysis and thus an abnormal reaction in the marrow or that they destroy both circulating red cells and developing cells in the marrow, thereby producing hyperplasia or other abnormal forms of marrow. The following recommendations are made regarding treatment: removal from exposure to toxic substances, especially those containing the benzene ring; an adequate diet containing meat, fresh fruit, vegetables and milk, with daily supplements of vitamin B in large amounts (90 to 120 Gm. of bakers' yeast); repeated blood transfusions, and splenectomy in some cases. Removal of the spleen should be performed in patients who have a marrow of the partially cellular type and in whom hemolysis is accelerated, as indicated by increased excretion of urobilinogen, a high reticulocyte count and the quick disappearance of the effects of transfusion.

Doan<sup>186</sup> has written a valuable and practical article dealing with the differential diagnosis and treatment of those nonhemolytic states which fail to respond to adequate liver or iron therapy. According to the author, most of these anemias can be placed in one of two general categories, according to the underlying pathologic condition of the bone marrow: (1) hypoplastic (aplastic) anemia or (2) myelophthistic anemia. The hypoplastic anemias usually involve all of the marrow elements, namely, erythrocytes, granulocytes and thrombocytes. The diagnosis should be reserved for cases in which decreased marrow activity underlies the peripheral blood changes. He discusses at considerable length the causation of this type of anemia and emphasizes that the incidence of idiopathic aplastic anemia is becoming less as the number of known chemicals and toxins potentially depressant to the marrow increases. Fourteen criteria for the diagnosis of the condition are named, as follows: a history of exposure to toxic medicinal or industrial agents; no weight loss or anorexia; normal basal metabolic rate; hypochlorhydria; minimal adenopathy; no splenomegaly; granulocytopenic leukocytopenia; no immature myelocytes; thrombopenia with purpura, an early prominent sign; normochromic, normocytic anemia; an absolute decrease in reticulocytes; normal red cell fragility; high level of plasma iron, and panhypoplasia of the sternal marrow. Among the etiologic agents, he emphasizes especially the following overwhelming infection with various bacteria; industrial chemicals and therapeutic agents, such as arsenicals, gold and roentgen rays, and the relation of diet, its transformation, absorption and utilization. He also discusses myelophthistic anemia, which is defined as a slowly progressive anemia due to the therapy-resistant gradual invasion of the bone marrow by foreign cells at the expense of normal erythropoiesis. Osteosclerosis, plasma cell multiple myeloma, metastatic carcinoma, lymphosarcoma, Hodgkin's disease, miliary tuberculosis and the subleukemic types of myeloid, lymphoid and monocytic leukemia represent the more commonly encountered myelophthistic entities. He presents the following diagnostic criteria for myelophthistic anemia: deep bone pain with nocturnal exacerbations; bone erosion as shown by roentgen examination; loss of weight with progressive cachexia; increased basal metabolic rate (leukemias); free hydrochloric acid present in the gastric secretions, except in carcinoma of the stomach; possible presence of Bence-Jones protein in the plasma and urine in multiple myeloma; possible presence of granulocytopenia with immature myelocytes; presence or absence of invading foreign cells

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186. Doan, C. A.: The Differential Diagnosis and Treatment of Those Non-hemolytic Anemic States Failing to Respond to Adequate Liver or Iron Therapy, *J. Missouri M. A.* **38**:393, 1941.

in the peripheral blood (plasma cells, lymphosarcoma cells, leukemia cells); late occurrence of thrombopenia with purpuric manifestations; normocytic, orthochromic anemia; frequent increase in reticulocytes and possible presence of nucleated red cells in the circulating blood; increased sedimentation rate; normal or moderately increased red cell fragility, and foreign cell hyperplasia of the sternal marrow.

Mirick<sup>187</sup> considers that recovery from "idiopathic" aplastic anemia is rare, and he cites Wintrobe as finding only 6 cases in his review of the literature. For this reason he reports what he regards as the seventh case of cure. His patient was a 30 year old man who presented the classic manifestations of the disorder. The erythrocyte count, when first observed, was 1,410,000 per cubic millimeter. The percentage of polymorphonuclears was 30, and the platelets numbered 21,150 per cubic millimeter. Bone marrow obtained by sternal puncture was reported as showing "aplasia of the marrow." The patient displayed evidences of secondary thrombopenic purpura, gangrenous stomatitis and the effects of severe anemia. During the first eight months in the hospital, the course was exceedingly stormy. He received forty-one blood transfusions in the first nine months, totaling 20 liters of citrated blood. Other therapeutic measures consisted of a high vitamin diet, ferrous sulfate, 100 Gm. of raw liver daily and 3 Gm. of brewers' yeast daily during convalescence. The patient returned to work "apparently cured," eighteen months after his first entry and twenty-one months after the onset of the disease. Although his blood returned to normal in all other respects, the reticulocytes persisted at a level between 5 and 10 per cent for one year, and the platelets have fluctuated between 50,000 and 150,000 per cubic millimeter.

#### AGRANULOCYTOSIS

As the result of an unfortunate oversight, the important monograph on agranulocytosis by Plum,<sup>188</sup> published in 1937 and translated into English by Anderson, escaped mention in previous reviews. This publication of 410 pages is the most authoritative and comprehensive discussion of agranulocytosis available and should be consulted by all those who are interested in the disease. The bibliography of four hundred and twenty-two articles in various languages consists of a careful compilation of papers dealing with the subject. '

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187. Mirick, G. S.: Idiopathic Aplastic Anemia with Recovery. *Ann. Int. Med.* **14**:2307, 1941.

188. Plum, P.: *Clinical and Experimental Investigations in Agranulocytosis with Special Reference to the Etiology*, Copenhagen, NYT Nordisk Forlag, Arnold Busck, 1937.

Lawrence<sup>189</sup> outlines the following possible conditions which may contribute to the development of leukocytopenia:

1. Diminished manufacture of white cells. This may result from (a) simple inhibition, (b) maturation arrest, (c) aplasia of the bone marrow and (d) infiltration of the bone marrow with foreign cells.

2. Increased elimination of white cells. This might occur when large quantities of cells are poured into an infected area, such as an empyema, or when cells in large numbers are lost through normal channels, such as the gastrointestinal tract, the lungs, the spleen or the liver.

3. Increased destruction in the peripheral blood due either to an abnormal condition of the white cells or to pathologic substances in the circulating blood which cause destruction of the white cells.

4. Redistribution of the white cells in the vascular channels, such as occurs after the injection of foreign proteins.

5. Redistribution of the white cells in the body as a whole, as is seen in leukocytopenic phases of leukemia.

During a physiologic study of sharecroppers in Mississippi, it was noted by Forbes, Johnson and Consolazio<sup>190</sup> that a majority of the Negroes had leukocytopenia with related neutropenia, whereas white persons living under the same conditions had normal white cell counts. The average leukocyte count of 23 Negroes was 4,050 cells per cubic millimeter, whereas the average count of 7 white persons living under the same conditions and partaking of the same diet was 7,600 per cubic millimeter. Some of the percentages of polymorphonuclears in the Negroes were as low as 22 and 34. The administration of iron to 18 Negroes for twelve to sixteen days produced an increase in the average absolute number of neutrophils from 1,546 to 2,700 per cubic millimeter. The authors offer the following suggestions as an explanation of this effect of iron: These low counts are normal for Negroes, and the metal artificially stimulates the bone marrow to a general hyperactivity or perhaps irritates the intestines and so causes leukocytosis. Another point of view is that the leukocytopenia is abnormal and that the iron or some contaminant associated with it makes up a deficiency in the diet.

Leser<sup>191</sup> has written a general article on agranulocytic angina which covers adequately the various points in the etiology, diagnosis, pathology, prognosis and treatment of the condition. He emphasizes that in addi-

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189. Lawrence, J. S.: Leukopenia: A Discussion of Its Various Modes of Production, *J. A. M. A.* **116**:478 (Feb. 8) 1941.

190. Forbes, W. H.; Johnson, R. E., and Consolazio, F.: Leukopenia in Negro Workmen, *Am. J. M. Sc.* **201**:407, 1941.

191. Leser, R. U.: Agranulocytic Angina, *J. Indiana M. A.* **34**:64, 1941.

tion to aminopyrine, dinitrophenol, organic arsenicals, benzene and excessive irradiation, the sulfanilamide drugs must be included as a cause of the disease. For treatment, in addition to general measures, he recommends (1) intensive parenteral liver therapy and administration of liver by mouth, if possible; (2) repeated daily blood transfusions of 200 to 300 cc., and (3) pentnucleotide therapy, 10 cc. four times daily to be given intramuscularly or intravenously. We agree in general with these recommendations but dissent vigorously from advising the injection of pentnucleotide intravenously on account of ensuing severe reactions.

Muether, Moore, Stewart and Broun<sup>192</sup> report a case of granulocytopenia which they attribute to excessive splenic lysis. After splenectomy the patient made a complete recovery for at least the period of observation of fourteen months. According to these authors, this syndrome was first described by Wiseman and Doan in 1939 as characterized by splenic enlargement, peripheral granulocytopenia and myeloid hyperplasia. The mode of production of this disorder is strikingly different from that of other types of granulocytopenia, as there is excessive destruction of the neutrophils by the macrophages in the spleen, and the bone marrow shows myeloid hyperplasia, which is regarded as compensatory. Their patient, a woman aged 31, had experienced five episodes of acute pain in the left upper quadrant of the abdomen, fever and prostration, which was associated with a steady drop in leukocytes and finally a complete disappearance of granulocytes from the circulating blood. These attacks usually appeared without obvious cause, but it is of interest to note that they had also occurred on two occasions after the administration of aminopyrine. The diagnosis of this syndrome, according to the authors, should not be difficult, as it rests on the presence of a hyperplastic bone marrow and an abnormal diminution of granulocytes in the peripheral blood. On removal of the spleen in this patient, it was found to be three times its normal size and to weigh 325 Gm. The most striking feature on microscopic examination was the presence of large numbers of neutrophils in the splenic pulp which were irregularly distributed and in focal accumulations. It is known that one function of the spleen is the destruction of effete granulocytes. The authors postulate that this syndrome may be produced by hyperfunction of the spleen in phagocytosing essentially normal neutrophils or that some error in development of the granulocytes exists and that as a result they are selectively removed by the spleen.

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192. Muether, R. O.; Moore, L. T.; Stewart, J. W., and Broun, G. O.: Chronic Granulocytopenia Caused by Excessive Splenic Lysis of Granulocytes: Report of a Case, *J. A. M. A.* **116**:2255 (May 17) 1941.

Nordenson and Röden<sup>193</sup> present a case of a woman aged 50 who had the usual picture of chronic arthritis, a chief complaint of persistent fatigue and chronic granulocytopenia of four years' duration. The bone marrow showed myeloid hyperplasia which the authors attributed to maturation arrest; the spleen was not palpable. During the course of four years the patient was treated with nucleic acid preparations, liver extract, iron, roentgen rays, etc., which did not produce a beneficial effect. On the basis that the patient had a hyperplastic marrow and that splenectomy might release a fuller and more effective production of cells in the marrow, this operation was performed. After the procedure, there was a prompt and dramatic improvement, and when examined four months later, the patient's blood did not show any pathologic changes. Apparently this case is similar to the one just described.

Kopp<sup>194</sup> reports the case of a 49 year old man who had pronounced leukopenia, as evidenced by a white cell count which was usually below 2,000 per cubic millimeter, with a polymorphonuclear leukocyte percentage which varied between 45 and 62. The condition was asymptomatic during a four year period of observation but terminated in the typical clinical picture of agranulocytic angina. Various etiologic possibilities were considered, but none was proved. The author believes that this supports the theory that agranulocytic angina tends to occur in one in whom a bone marrow dyscrasia is already present.

Davies and Wingfield<sup>195</sup> investigated the effect of injections of epinephrine on the agranulocytosis which sometimes is associated with kala-azar. They cite Zia and Forkner as stating in 1932 that chronic granulocytopenia is the rule in kala-azar. The opinion has been expressed that the anemia of the disease is myelophthisic in nature, and Zia and Forkner considered that the extreme leukopenia and the total absence of granulocytes in certain cases might be, in part at least, the result of this same process. The patient studied by Davies and Wingfield had a leukocyte count as low as 1,400 cells per cubic millimeter, with 1 per cent polymorphonuclears. He was treated with parenteral administration of nucleic acid pentnucleotide and blood transfusion, without effect. After subcutaneous injections of epinephrine, however,

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193. Nordenson, N. G., and Röden, S.: Chronic, Malignant Granulocytopenia Treated with Splenectomy, Recovery: Report of Case, *Acta chir. Scandinav.* **84**: 519, 1941.

194. Kopp, I.: Chronic Leukopenia with Fatal Termination Due to Agranulocytic Angina: Case Report, *Am. J. Orthodontics (Oral Surg. Sect.)* **27**:245, 1941.

195. Davies, A., and Wingfield, A.: Agranulocytosis in Kala-Azar and Use of Adrenalin, *Tr. Roy. Soc. Trop. Med. & Hyg.* **34**:421, 1941.



there was a transient increase in the polymorphonuclears, which began within a few minutes after the drug was given. They conclude that the frequent repetition of epinephrine injections cured the patient, who had failed to respond to other forms of treatment.

A case of unusual interest of sensitivity to aminopyrine is reported by Alvarez.<sup>106</sup> The patient, a woman aged 30, complained of repeated brief attacks characterized by a severe chill, followed by high fever, headache and pain in the muscles and joints. She associated these episodes with her menstrual periods, but her physician made a diagnosis of malaria because she had recently been in the West Indies. Alvarez observed the patient in an attack in which the chill was so severe that it shook the bed and persisted for an hour. This was followed by a rise in temperature to 103 F., after which it soon returned to normal. During the febrile episode, the leukocyte count fell to 1,400 per cubic millimeter and the lymphocyte percentage rose to 45. The patient admitted that she had taken aminopyrine just prior to the attack. A discontinuance of the drug was followed by disappearance of the acute episodes. According to Alvarez, these symptoms resembled those induced by the injection of foreign protein.

Semon<sup>107</sup> reports the case, with recovery, of a 62 year old male physician who presented the characteristic clinical picture of agranulocytic angina after the administration of 7.6 Gm. of "a well known sulfonamide preparation." Rinkoff and Spring<sup>108</sup> state that from January 1939 to February 1941 in the Bronx Hospital, New York, 768 patients received sulfanilamide and its related compounds. Of these, granulocytopenia developed in 5, an incidence of 0.65 per cent. They conclude that these drugs may have a toxic effect on the bone marrow, and hence their use is contraindicated in minor ailments. Furthermore, they caution that frequent blood examinations should be made not only while the drug is being given but for five to ten days after it has been discontinued. The authors state, in conclusion, that while a small dose may cause leukocytopenia or fatal agranulocytosis, the toxic effects on the bone marrow usually manifest themselves after prolonged use. Goldman, Applebaum and Antopol<sup>109</sup> report 2 fatal cases of agranulocytosis

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196. Alvarez, W. C.: Chills and Fever Produced by Amidopyrine, Proc. Staff Meet., Mayo Clin. **16**:760, 1941.

197. Semon, H. C.: Agranulocytosis with Angina Following Sulfonamide Treatment, Brit. M. J. **2**:668, 1940.

198. Rinkoff, S. S., and Spring, M.: Toxic Depression of the Myeloid Elements Following Therapy with the Sulfonamides: Report of Eight Cases, Ann. Int. Med. **15**:89, 1941.

199. Goldman, L. M.; Applebaum, I., and Antopol, W.: Malignant Neutropenia Following the Use of Sulfapyridine, Am. J. Clin. Path. **11**:810, 1941.

following the administration of sulfapyridine and present pertinent information abstracted from the literature. An analysis of data obtained from 30 published cases (including the 2 just mentioned) shows that 43 per cent of the patients in whom agranulocytosis developed after the administration of sulfapyridine had discontinued the drug and then reinstituted its use. Of the remaining patients, 37 per cent received continuous treatment for ten or more consecutive days, and only 20 per cent received the drug for less than ten consecutive days. Of the 12 previously reported fatal cases, in only 1 was the patient exposed to the drug for less than ten days. It is considered by the authors that the occurrence of the majority of cases of agranulocytosis after an irregular or prolonged course of drug administration may possibly be explained on the basis of an allergic reaction. A case of agranulocytosis and hepatitis following the treatment of urethritis with sulfapyridine is reported by Finger.<sup>200</sup> The total amount of the drug administered is not given, as it is merely cited that he had received "about 60 tablets of M. & B. 693." Although the leukocyte count rose satisfactorily after the injection of pentnucleotide solution, the patient died on the fifth day of his acute illness. Morris<sup>201</sup> reports a case of agranulocytosis with an onset of acute abdominal pain. The patient, a man aged 21, was given 63 Gm. of sulfapyridine in two courses over a period of eighteen days as treatment for gonorrhea. Nine days after the drug had been discontinued, he experienced acute pain in the upper portion of the abdomen which settled in the right iliac fossa. The body temperature was 104.8 F. A diagnosis of acute appendicitis was made, and an appendectomy was done. The proximal portion of the appendix contained some mucopurulent material, and submucous hemorrhages were present for about 1 inch (2.5 cm.) of the wall. The pus was examined microscopically and found to contain a number of poorly staining mononuclear cells. No polymorphonuclear cells were seen. On the following day the white cell count was 800 per cubic millimeter, with only 1 per cent granular cells. Recovery followed treatment with yellow bone marrow and pentnucleotide. Pearson and Lewis<sup>202</sup> report a case of agranulocytosis following the administration of 43 Gm. of sulfapyridine in eighteen days. Recovery followed the use of sodium nucleinate and pentnucleotide despite the fact that the patient had complete agranulocytosis for two days. Three cases of

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200. Finger, A.: Agranulocytosis and Hepatitis Following Sulphapyridine Treatment, *M. J. Australia* 1:760, 1941.

201. Morris, G. N.: Agranulocytosis Following the Use of "M & B 693," with the Report of a Case Associated with Abdominal Symptoms, *M. J. Australia* 1:515, 1941.

202. Pearson, J. E. G., and Lewis, A. A. G.: Agranulocytosis After Sulphapyridine Therapy, with Recovery, *Lancet* 2:779, 1940.

granulocytopenia are described by Strong,<sup>203</sup> in which he attributes the condition primarily to infection. One patient, a girl aged 4 months, had bilateral otitis media with mastoiditis, and an absolute polymorphonuclear count of 600 per cubic millimeter developed. After pentnucleotide was administered, the leukocyte count rose to normal. It again fell to an abnormally low level following the discontinuance of the drug. A second patient, a girl aged 1 year, had an acute infection of the upper respiratory tract. The leukocyte count was 2,400 per cubic millimeter, with 38 per cent of polymorphonuclears, and the absolute polymorphonuclear count fell to 900 cells per cubic millimeter after sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) was given. The leukocyte count returned to normal after the discontinuance of the drug and the administration of pentnucleotide. A third patient, a boy aged 8 months, with bilateral otitis media, was treated with sulfathiazole; granulocytopenia developed, as indicated by an absolute polymorphonuclear count of 1,530 per cubic millimeter. This depression of the leukocyte count was attributed to the infection and the chemotherapy. The white cell count returned to normal after injections of pentnucleotide. Subsequently, an infection of the respiratory tract developed, and at this time the absolute polymorphonuclear count fell to 400 cells per cubic millimeter. The author suggests that particular care be taken in the administration of chemotherapeutic agents to infants whose bone marrow is already depressed by infection. The belief is set forth that merely discontinuing the drug will cause a return of the polymorphonuclears to normal but that pentnucleotide therapy accelerates the rate of recovery of the bone marrow. A case of agranulocytosis in an infant approximately 1 year of age is reported by Barlow.<sup>204</sup> The patient was given 1.25 Gm. of sulfapyridine on account of acute otitis media and evidence of an inflammatory reaction about the left knee joint. Five days after the administration of the drug had been begun, the patient was admitted to the hospital, at which time it was found that the red cell count was 930,000 per cubic millimeter; the hemoglobin concentration, 18 per cent, and the white cell count, 12,000 per cubic millimeter. No granulocytes could be found, and 93 per cent of the white cells were small lymphocytes, 5 per cent were large lymphocytes and 2 per cent were classified as lymphoblasts. It should be noted that there was evidence that the child was anemic before the sulfapyridine therapy was instituted. Such a picture suggests the diagnosis of lymphatic leukemia. After treatment with pentnucleotide

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203. Strong, P. S.: Granulocytopenia: Report of Three Cases in Which the Condition Was Due to Infection and in Which Chemotherapy Was Employed, *Am. J. Dis. Child.* **61**:445 (March) 1941.

204. Barlow, H. C.: A Case of Agranulocytosis in an Infant: Recovery, *Brit. M. J.* **1**:669, 1941.

and two blood transfusions, however, the patient made a complete recovery and the blood was restored to normal.

The first report of a case of agranulocytosis following the administration of sulfathiazole was published by Kennedy and Finland.<sup>205</sup> The patient was a female aged 38 who was suffering from subacute bacterial endocarditis. Toward the end of the third week of treatment with sulfathiazole, at which time it was estimated that the patient had received approximately 125 Gm. of the drug, the characteristic evidence of acute agranulocytosis appeared. Death followed, despite a blood transfusion and administration of 10 cc. of liver extract and 30 cc. of pentnucleotide. The appearance of characteristic, though mild, rash, followed shortly thereafter by high fever, complete absence of granulocytes and a marked drop in other leukocytic elements of the peripheral blood, leaves little doubt that the patient had acute agranulocytosis resulting from sulfathiazole therapy, although the patient had also received sulfapyridine for two days prior to the use of sulfathiazole. It is stated by Hoyne and Larimore<sup>206</sup> that the toxic manifestations following the use of sulfathiazole have been less than those encountered with some of the other derivatives of sulfanilamide. The authors believe that their case is the first fatality reported in which agranulocytosis could be attributed to sulfathiazole alone. Their patient, a man of 34 years, took an estimated 100 Gm. during a period of nearly two months as treatment for gonorrhea. The characteristic clinical picture of acute agranulocytosis was presented by the patient on admission to the hospital, and death ensued nine hours later. Pippin<sup>207</sup> reports 2 cases of drug fever and 1 of agranulocytosis due to sulfathiazole therapy. He states that drug fever following the use of sulfathiazole is more common than is generally supposed, with an incidence of 6 to 15 per cent in the different series reported. This type of fever is an ominous sign as it portends grave complications, such as hemolytic anemia, agranulocytosis and toxic hepatitis. A cutaneous rash, he points out, is often the first sign of toxicity. He emphasizes that acute hemolytic anemia may develop in the first twenty-four to seventy-two hours of treatment, and agranulocytosis more often occurs after about two weeks. A slowly developing anemia over a period of a week is of little consequence. Finally, he cautions that the sulfanilamide compounds should not be prescribed for

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205. Kennedy, P. C., and Finland, M.: Fatal Agranulocytosis from Sulfathiazole, *J. A. M. A.* **116**:295 (Jan. 25) 1941.

206. Hoyne, A. L., and Larimore, G. W.: Sulfathiazole as a Cause of Death: Report of Patient with Acute Agranulocytosis, *J. A. M. A.* **117**:1353 (Oct. 18) 1941.

207. Pippin, B. I.: Staphylococcemia and Agranulocytosis: Report of Three Cases, with Special Reference to Drug Toxicity, *Wisconsin M. J.* **40**:194, 1941.

patients outside the hospital unless it is possible to observe them frequently.

Granulocytopenia attributable to sulfadiazine (2-[paraaminobenzene-sulfonamido]-pyrimidine) therapy had not been noted in the literature prior to Jan. 1, 1942. The following case, however, was observed at the University of Michigan Hospital.<sup>208</sup> The patient, a man of 70 years, had undergone a resection of a gangrenous ileum in a strangulated right inguinal hernia twenty-seven days before his death. He received a total of 76 Gm. of sulfadiazine during a period of nineteen days, before a fatal termination occurred from agranulocytosis. There had been no previous administration of sulfanilamide drugs.

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208. Levin, M., and Bethell, F. H.: Fatal Granulocytopenia Developing During the Administration of Sulfadiazine, Univ. Hosp. Bull., Ann Arbor 8:30, 1942.

*(To Be Concluded)*

## Correspondence

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### CONCENTRATION OF SULFANILAMIDE IN BODY FLUID

*To the Editor:*—Since the article in the March number entitled "Effect of Inflammation on the Concentration of Sulfanilamide in Pleural and Joint Fluids" by Raymond Gregory (ARCH. INT. MED. 69:429, 1942) leads to some rather startling conclusions, I should like to make a few comments on it.

It is difficult to understand how a freely diffusible substance like sulfanilamide would concentrate in a purulent effusion. Dr. Perrin Long several years ago made the same—and to him startling—discovery that the level of the drug in the body fluid was extremely high in relation to its level in the blood stream. However, a little further investigation soon revealed that the apparently high level in the body fluid was due to the procaine hydrochloride used for local anesthesia during withdrawal of the fluid. Many persons erroneously assume that because a method is described for the determination of sulfanilamide it is necessarily specific. The same color reaction can be given by a number of compounds which resemble sulfanilamide in their chemical structure. For example, with the method of Marshall, Emerson and Cutting, a solution of paraaminobenzoic acid containing 50 mg. per hundred cubic centimeters will give an apparent concentration of 37.2 mg. of sulfanilamide per hundred cubic centimeters, and a solution of procaine hydrochloride containing 50 mg. per hundred cubic centimeters will give a color intensity equal to a concentration of 15.5 mg. of sulfanilamide per hundred cubic centimeters. The method of Marshall, Emerson and Cutting is therefore not specific, and its accuracy in determining the amount of sulfanilamide in the blood depends on the fact that compounds giving the same color reaction are normally not present.

Since it is probable that Dr. Gregory used procaine hydrochloride in tapping the pleural cavity and the joints in his patients, it seems to me likely that this is the main source of error in his work. He may be right, but on the basis of his published work his conclusions are open to grave doubt, and they are dangerous in that they give a sense of security to physicians who are treating patients with serious infections with inadequate doses of sulfanilamide and its derivatives.

Peter Bent Brigham Hospital.

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### CHEMICAL FACTORS IN THE FORMATION OF GALLSTONES

*To the Editor:*—In the November issue (Chemical Factors in the Formation of Gallstones, ARCH. INT. MED. 65:1037, 1941) Dr. Louis Bauman and Dr. Joseph T. Bashour questioned certain aspects of the investigations reported by us regarding the solubility of the cholesterol in gallstones. We should like to clarify the points raised in their discussion.

We reiterate that our experiments as well as those of Walsh and Ivy have shown that the solvent capacity of bile for cholesterol lies to a great extent, although not exclusively, in what has been termed the saponifiable, or "fatty acid," fraction of bile. By the latter term is meant the material obtained by acidifying

and extracting with a suitable fat solvent the portion of the bile that has been treated with alcoholic potassium hydroxide and from which all of the nonsaponifiable matter has been removed. Obviously, bile salts are not present in this fraction, designated as the alcohol-soluble saponifiable fraction, after such treatment.

A second point questioned was the conclusion made relative to the molar concentration of fatty acids, i. e., that in a previous publication (Dolkart, R. E.; Jones, K. K., and Brown, C. F. G.: *Chemical Factors Concerned in the Formation of Gallstones*, *ARCH. INT. MED.* 62:618 [Oct.] 1938) some of us had stated that since there was no apparent correlation between solvent action and molar concentration of the different fatty acids, the solvent effect was chiefly a chemical phenomenon. This assertion was made on the basis that the solvent effects ascribable to physical and mechanical action alone had been shown to be negligible when the data were recalculated in terms of molar concentration.

With regard to the species differences noted in the incidence of gallstone formation, our information based on analyses of ox and hog gallstones indicates that their cholesterol content, although not approximating that of human stones, nonetheless forms the framework of the stones.

We cannot account for the lack of agreement between data obtained by Bashour and Bauman and our own on the solubility of cholesterol in solutions of bile salts. One factor may be the fatty acid complex that is present in many of the so-called purified bile salts. It is interesting to note that A. Rosin, whose observations are cited by Bauman and Bashour in support of their views, based her conclusions on the solubility of cholesterol in bile salts on data obtained in six separate experiments involving the re-use of the same cholesterol gallstone.

That the solubility studies carried out at 70 C. were not physiologic we are quite aware, but the purpose of these *in vitro* studies was not to duplicate conditions in the gallbladder, rather to obtain comparable data on the solubility of cholesterol in the different fatty acids. At this temperature the difficulty of obtaining solutions rather than soapy suspensions was circumvented, and we believe the comparable results to be of value.

The question of cholesterol crystallization in bile has only been opened, not answered, by the work of Bauman and Bashour, our own studies or the contributions of numerous other investigators. From our viewpoint the role of the fatty acids in maintaining cholesterol in solution seems at present the most fruitful line of investigation.

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## News and Comment

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**American Diabetes Association.**—The second annual meeting of the American Diabetes Association will be held at Haddon Hall, Atlantic City, N. J., Sunday, June 7. The morning program will consist of a business meeting, following a 9 o'clock breakfast, an address by the president, a round table discussion presided over by Dr. Herman C. Mosenthal and the showing of an educational film on diabetes. At the afternoon session, which will be called at 2 o'clock, six, and possibly eight, papers will be presented on subjects related to diabetes. At the evening session, following dinner, Dr. William Muhlberg will deliver the Banting Memorial Lecture, entitled "An Analysis of Statistics Bearing on Diabetes Mellitus."



## Book Reviews

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**The Doctors Mayo.** By H. B. Clapesattle. Price, \$3.75. Pp. 822. Minneapolis: The University of Minnesota Press, 1941.

Whatever the ultimate appraisal of this book on the Doctors Mayo, it is clear that Miss Clapesattle has made a notable contribution to medical biography. Throughout the eight hundred odd pages of detailed material, which would do credit to a standard nineteenth century double-decker, interest never flags. This is partly to be credited to Miss Clapesattle's simple and vivid style, but even more to her subject, which contains all the elements of biographic drama. Full of color is the description of pioneer days in the Middle West and of country practice in Minnesota as built up around the "old doctor." But the accession of the two young physicians—Dr. Will and Dr. Charlie—and the story of the development of their monumental achievement become downright thrilling. It is especially interesting to have set forth the true account of the tornado and the beginnings of St. Mary's Hospital—events which have become much distorted by popular legend—and to learn of the orderly and inevitable flowering of this modest project into the vast Mayo Clinic.

Dr. Will and Dr. Charlie were great men on any count—of this there can be no doubt—but one wonders whether Miss Clapesattle has not fallen a little into that distemper of which Macaulay accused Boswell and of which other great biographers, including Lockhart, Southey, Trevelyan and Harvey Cushing, were not entirely free.

It is a pity that in listing the achievements of the Mayo Clinic more critique is not exercised at some points. In the reviewer's mind, to mention one example, the less said the better about streptococcus vaccine as a prophylactic measure against influenza. Also in tracing the development of the personnel of the institution one is surprised, in view of the enumeration of many lesser lights, to find no mention of several staff members for years outstanding in internal medicine, whose work has redounded greatly to the reputation of the Clinic.

To the reviewer the earlier history of the doctors is the most vivid and exciting part; despite their later astonishing achievements, a feeling that things are less real, that Dr. Will and Dr. Charlie are already legendary figures creeps in. One is almost disappointed to find them in grand but perfectly conventional surroundings, to read of yachts and winter homes in Tucson; of secretaries galore, and of chauffeurs who follow along the river bank with the motor to rush the doctor home to Rochester in case of an important call.

Finally, Miss Clapesattle is to be congratulated on the interesting way in which she has intertwined the personal story of the Mayos with the history of modern surgery. This makes good and useful reading for every physician and medical student.

## INTERMEDIATE ACTION OF MIXTURES OF SOLUBLE INSULIN AND PROTAMINE ZINC INSULIN

ARTHUR R. COLWELL, M.D.

JOSEPH LEWIS IZZO, M.D.

AND

WALTER A. STRYKER, PH.D., M.D.

EVANSTON, ILL.

From the standpoint of clinical usefulness in cases of severe diabetes neither of the two standard insulins, soluble insulin and protamine zinc insulin, is ideal for routine day by day use. Because it is in solution, ordinary insulin is absorbed rapidly and within a short time exerts a strong effect which fades quickly. Hence it must be given frequently, and in excess it tends to cause violent hypoglycemic symptoms. With soluble insulin alone it is impossible to control severe diabetes in many cases unless multiple daily injections are given, including one during the normal sleeping hours. The same is true of solution of zinc insulin crystals, or crystalline insulin, the action of which is practically identical with that of ordinary insulin.<sup>1</sup>

Protamine zinc insulin eliminates some of these disadvantages because it releases insulin slowly. Its effects are slow in onset, weak until reenforced by repeated overlapping doses but slow to disappear.<sup>2</sup> Hence, even severe diabetes can be better controlled by injections given

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From the Department of Medicine, Northwestern University Medical School, and Evanston Hospital.

1. Jackson, R. L., and Boyd, J. D.: Relative Efficiency of Commercial Forms of Insulin, *Proc. Soc. Exper. Biol. & Med.* **41**:15-16 (May) 1939. Marble, A., and Vartiainen, I.: Crystalline Insulin, *J. A. M. A.* **113**:1303-1309 (Sept. 30) 1939. Ricketts, H. T., and Wilder, R. M.: Solutions of Amorphous Insulin and Solutions of Zinc Insulin Crystals: Clinical Studies of Comparative Speed and Duration of Action, *ibid.* **113**:1310-1312 (Sept. 30) 1939. Duncan, G. G.; Cuttle, T. D., and Jewesbury, E. C. O.: Observations on Comparative Clinical Values of Zinc Insulin Crystals in Solution and Unmodified Insulin, *Bull. Ayer Clin. Lab Pennsylvania Hosp.* **3**:293-306 (Dec.) 1939.

2. Wilder, R. M., and Wilbur, D. L.: Diseases of Metabolism and Nutrition: Review of Certain Recent Contributions, *Arch. Int. Med.* **59**:329-337 (Feb.) 1937.

once daily; hypoglycemia is not so violent or frequent; glycosuria during overnight fasting is modified; sudden acidosis is less likely to occur with delays in its administration, and general health and nutrition are better because of its more sustained action.<sup>3</sup> Yet it possesses two major disadvantages, both due to slow or uncertain absorption. First, there are inconsistencies in the responses to repeated daily doses of the same size, probably due to variations in the rates of solution and absorption of insulin from different depots. This produces an undulating form of control, with unpredictable waves of glycosuria and of hypoglycemia.<sup>4</sup> Second, in cases of severe diabetes doses of protamine insulin sufficiently large to control the glycosuria following generous carbohydrate meals are likely to cause hypoglycemic shock during the night period of fasting. Doses small enough to avoid nocturnal hypoglycemia tend to permit heavy glycosuria after meals.<sup>5</sup>

The combined use of both standard insulins stands out as the method of therapy which most uniformly avoids the problems inherent in treatment with either type of insulin alone. Most often this is accomplished by injection of one large dose of protamine zinc insulin daily and one or two supplementary smaller doses of soluble insulin.<sup>6</sup> Thus, the prolonged, fairly uniform action of protamine zinc insulin in an amount sufficient to control nocturnal glycosuria is supplemented by small doses of soluble insulin which modify the heavier glycosuria following meals and fade out during the night when not needed. Probably combined treatment with both types of insulin injected separately is the most common in use today by patients with severe diabetes. Its rationale has recently been considered in illuminating detail by Peck.<sup>7</sup>

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3. Joslin, E. P.: Protamine Insulin and Its Advantages, *New England J. Med.* **215**:1166-1168 (Dec. 17) 1936.

4. Joslin, E. P.: Difficulties in the Use of Protamine Zinc Insulin, *J. A. M. A.* **110**:90-91 (Jan. 8) 1938. Kepler, E. J.: Clinical Experience with Protamine Zinc Insulin, *ibid.* **110**:92-96 (Jan. 8) 1938. Mark, M. F.: Optimum Time for Administration of Protamine Zinc Insulin, *Arch. Int. Med.* **64**:897-906 (Nov.) 1939.

5. Lawrence, R. D., and Archer, N.: Some Experiments with Protamine Insulinate, *Brit. M. J.* **1**:747-749 (April 11) 1936.

6. (a) Campbell, W. R.; Fletcher, A. A., and Kerr, R. B.: Protamine Insulin in the Treatment of Diabetes Mellitus, *Am. J. M. Sc.* **192**:589-600 (Nov.) 1936. (b) Joslin, E. P.; Root, H. F.; Marble, A.; White, P.; Joslin, A. P., and Lynch, G. W.: Protamine Insulin, *New England J. Med.* **214**:1079-1085 (May 28) 1936. (c) Joslin, E. P.: Protamine Insulin, *J. A. M. A.* **109**:497-503 (Aug. 14) 1937. (d) Warvel, J. H., and Shafer, M. R.: Protamine Insulin in the Treatment of Diabetes Mellitus, *J. Indiana M. A.* **30**:325-332 (July) 1937. (e) Mosenthal, H. O.: Protamine Zinc Insulin: Clinical Application, *J. A. M. A.* **110**:87-90 (Jan. 8) 1938.

7. Peck, F. B.: Therapeutic Application of the Various Insulins, *South. Med. & Surg.* **103**:539-545 (Oct.) 1941.

Although that method provides better control than the use of either insulin alone, multiple injections still are required. Many patients with more severe forms of diabetes still find it difficult to avoid intermittent hypoglycemia and glycosuria. Confusion is created by the use of two preparations with different properties. Most efforts to mix them have failed in their purpose, because a small proportion of soluble insulin is precipitated by the excess free protamine in protamine zinc insulin and its prompt effect is lost.<sup>8</sup>

#### MIXTURES OF SOLUBLE INSULIN AND PROTAMINE ZINC INSULIN

With few exceptions previous work with mixtures of the two standard insulins has been confined to uncritical use of them mixed in the proportions commonly employed in practice, i. e., large doses of protamine zinc insulin combined with smaller doses of insulin in the same ampule or syringe. Lawrence expressed the belief that mixtures containing as little as 12 units of soluble insulin in 40 units of protamine zinc insulin might lose some of the soluble insulin by precipitation<sup>9</sup> but retained the individual actions of both types of insulin.<sup>10</sup> Graham<sup>11</sup> used larger fractions of soluble insulin, but protamine zinc insulin was still in excess. Wilder and his associates advised against the use of such mixtures<sup>8</sup> but later "adopted this technic with results that are very satisfactory."<sup>12</sup>

A few investigators have attempted to avoid loss of soluble insulin on mixing by using a narrow bore<sup>6a</sup> or double-barrelled<sup>13</sup> syringe or by employing separate syringes attached successively to the same needle *in situ*.<sup>14</sup> These methods obviously do not avoid contact before or after injection and hence permit mixing in variable degrees.

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8. Sprague, R. G.; Blum, B. B.; Osterberg, A. E.; Kepler, E. J., and Wilder, R. M.: Clinical Observations with Insulin Protamine Compound, J. A. M. A. **106**: 1701-1705 (May 16) 1936.

9. Lawrence, R. D.: The Treatment of Insulin Cases by One Daily Injection, Acta med. Scandinav., 1938, supp. 90, pp. 32-53.

10. Lawrence, R. D.: Zinc-Protamine-Insulin in Diabetes: Treatment by One Daily Injection, Brit. M. J. **1**:1077-1080 (May 27) 1939.

11. Graham, G.: The Use of a Mixture of Ordinary and Protamine Insulin, Acta med. Scandinav., 1938, supp. 90, pp. 54-63.

12. Wilder, R. M.: Clinical Diabetes Mellitus and Hyperinsulinism, Philadelphia, W. B. Saunders Company, 1940, p. 92.

13. Watson, E. M.: A Double Syringe for the Administration of Protamine Zinc and Unmodified Insulin, Canad. M. A. J. **40**:72-73 (Jan.) 1939.

14. Campbell, W. R.: Some Difficulties in the Use of the Insulins in Diabetic Practice, Bull. New York Acad. Med. **15**:579-596 (Sept.) 1939. Starch in Gluten Bread-Mixtures of Different Types of Insulin, Queries and Minor Notes, J. A. M. A. **112**:871 (March 4) 1939.

More critical studies have shown that mixtures containing small amounts of soluble insulin act in a manner indistinguishable from that of protamine zinc insulin. Bjuggren<sup>15</sup> reported that the action of morning doses of ordinary mixtures was weaker during the day but stronger at night than that of separate doses of the same quantities, probably because part of the regular insulin was converted into protamine zinc insulin on mixing. A well controlled comparison by Masters<sup>16</sup> showed that such mixtures act like protamine zinc insulin. Hence, most authorities now are reluctant to use such mixtures and advise separate injections when both insulins are required in cases of severe diabetes.<sup>17</sup>

Some observers<sup>18</sup> obtained more consistent and encouraging results by increasing the proportions of soluble insulin in the mixtures. Ulrich<sup>19</sup> recognized the difficulties inherent in mixing the two standard types of insulin. The excess of free protamine in commercial protamine zinc insulin readily combines with soluble insulin added to it. Thus, the net result, up to a certain limit of added insulin, is conversion into protamine insulin, with action identical with the action of that substance. Ulrich secured some modification of effect by mixing the two types in equal proportions. When more than an equal amount of soluble insulin was added, unmistakable increases in prompt action were obtained, comparable to those resulting from large doses of protamine zinc insulin and smaller doses of soluble insulin injected separately. Mixtures containing three parts soluble insulin and two parts protamine zinc insulin seemed most promising for clinical use in suitable patients. The action of repeated doses was fairly consistent and predictable—in fact, more so than that of separate injection of the two components simultaneously.

#### OTHER INSULIN COMBINATIONS WITH SUSTAINED EFFECTS

Literally dozens of other insulin combinations with prolonged action have been described in the literature—most of them within the past six years. To undertake a critical appraisal of their merits would be impossible for lack of comparative data. Few have been compared with

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15. Bjuggren, S.: Question of Mixing Common Insulin with Protamine Zinc Insulin Before Injection, *Nord. med. (Hygiea)* **4**:3099-3101 (Oct. 14) 1939.

16. Masters, T. D.: The Use of the Newer Insulins, *Illinois M. J.* **78**:319-323 (Oct.) 1940.

17. Morris, N.: The Newer Insulins, *Glasgow M. J.* **133**:1-19 (Jan.) 1940. Watson, E. M.: Comparative Efficiency of Various Methods for Administering Insulin, *Canad. M. A. J.* **43**:444-447 (Nov.) 1940. Marble, A.: The Treatment of Diabetes with Diet and Insulin, *New England J. Med.* **224**:583-586 (April 3) 1941.

18. Wauchope, G. M.: Zinc Protamine Insulin and Soluble Insulin Interaction in Combined Doses, *Lancet* **1**:962-966 (May 25) 1940. Graham.<sup>11</sup>

19. Ulrich, H.: Clinical Experiments with Mixtures of Standard and Protamine Zinc Insulins, *Ann. Int. Med.* **14**:1166-1179 (Jan.) 1941.

each other, although many were compared with insulin or with protamine zinc insulin by a variety of methods. An excellent review of those studied before 1938 is contained in Jensen's monograph on insulin.<sup>20</sup> A summary of the types of combinations, their names, the dates of report, the investigators and the distinguishing characteristics is contained in table 1.

Originally, it was hoped that the addition of zinc would give a desirable intermediate action to soluble insulin. The introduction of solution of zinc insulin crystals was accompanied by claims of prolonged effect.<sup>22</sup> Undoubtedly, zinc lengthens slightly the duration of action both of soluble and of protamine insulin,<sup>23</sup> but the difference is not of practical importance. There is still a wide spread between the intensity and the duration of the action of the two standard types of insulin in spite of the addition of zinc. The chief value of solution of zinc insulin crystals lies in its freedom from foreign protein.

Histone insulin,<sup>24</sup> globin insulin<sup>25</sup> and acid, or clear, protamine insulin<sup>26</sup> are the modifications which appear most promising. A

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20. Jensen, H. F.: *Insulin: Its Chemistry and Physiology*, New York, Oxford University Press, 1938, pp. 97-103.

21. Footnote deleted by author.

22. Freund, H. A., and Adler, S.: Effects of Standard, Protamine and Crystalline Insulin on Blood Sugar Levels, *J. A. M. A.* **107**:573-577 (Aug. 22) 1936. Mains, M. P., and McMullen, C. J.: The Clinical Investigation of an Improved Crystalline Insulin: Preliminary Report, *ibid.* **107**:959-962 (Sept. 19) 1936.

23. (a) Scott, D. A., and Fisher, A. M.: Studies on Insulin with Protamine, *J. Pharmacol. & Exper. Therap.* **58**:78-92 (Sept.) 1936. (b) Kerr, R. B.; Best, C. H.; Campbell, W. R., and Fletcher, A. A.: Protamine Insulin, *Canad. M. A. J.* **34**:400-401 (April) 1936. (c) Rabinowitch, I. M.; Foster, J. S.; Fowler, A. F., and Corcoran, A. C.: Clinical Experiences with Protamine-Zinc-Insulin and Other Mixtures of Zinc and Insulin in Diabetes Mellitus, *ibid.* **35**:239-252 (Sept.) 1936. (d) Drysdale, H. R.: Protamine Insulin in Juvenile Diabetes: Clinical Observations, *J. A. M. A.* **108**:1250-1257 (April 10) 1937. (e) Smith, B., and Grishaw, W. H.: Survey of Diabetes: Statistical Data and Control Comparisons with Various Insulins, *Arch. Int. Med.* **66**:465-477 (Aug.) 1940.

24. (a) Bischoff, F.: Histone Combinations of the Protein Hormones, *Am. J. Physiol.* **117**:182-187 (Sept.) 1936. (b) Gray, P. A.; Bischoff, F., and Sansum, W. D.: Treatment of Diabetes Mellitus with Insoluble Insulin Compounds: Histone-Insulin, *Ann. Int. Med.* **11**:274-284 (Aug.) 1937.

25. (a) Reiner, L.; Searle, D. S., and Lang, E. H.: Insulin Preparations with Prolonged Activity: Globin Insulin, *Proc. Soc. Exper. Biol. & Med.* **40**:171 (Feb.) 1939. (b) Bauman, L.: Clinical Experience with Globin Insulin, *Am. J. M. Sc.* **198**:475-481 (Oct.) 1939. (c) Marks, H. E.: A New Globin Insulin, *M. Clin. North America* **24**:649-670 (May) 1940. (d) Duncan, G. G., and Barnes, C. E.: The Action of Globin Insulin Compared with That of Crystalline, Unmodified and Protamine Zinc Insulin, *Am. J. M. Sc.* **202**:553-563 (Oct.) 1941.

26. Warvel, J. H.: Protamine and Other Slow Acting Insulins and Their Clinical Application: Review of Medical Progress, Ohio State University College of Medicine, 1940, p. 140.

TABLE 1.—*Insulin Combinations with Sustained Effects*

Compound	Comment	Author
Lipoid Suspensions and Emulsions		
Metacholesterin, "oil," liquid petrolatum or hydrous wool fat and insulin	Viscous mixtures; uncertain absorption	Bernhardt and Strauch: <i>Ztschr. f. klin. Med.</i> <b>104</b> : 744, 1926
Arachis oil or castor oil and insulin	Viscous mixtures; uncertain absorption	Leyton: <i>Lancet</i> <b>1</b> : 756, 1929
Cholesterol and insulin	Uncertain action	Lange and Schoen: <i>Arch. f. exper. Path. u. Pharmacol.</i> <b>113</b> : 92, 1926 Surányi and Szalai: <i>Klin. Wehnschr.</i> <b>9</b> : 2159, 1930
Lecithin and insulin	Uncertain action	Surányi and Szalai: <i>Klin. Wehnschr.</i> <b>9</b> : 2159, 1930 Skouge: <i>Acta med. Scandinav. (supp.)</i> <b>50</b> : 232, 1932
Colloid system containing insulin (insulin-durant)	Two or three day hypoglycemic effects	Katsch, Scholderer and Klatt: <i>Ztschr. f. klin. Med.</i> <b>129</b> : 608, 1936 Klein and Grosse: <i>Ztschr. f. d. ges. exper. Med.</i> <b>98</b> : 623, 1936 Störriing: <i>Med. Klin.</i> <b>1</b> : 369, 1937
Colloid Combinations		
Acacia and insulin	Some prolongation of effect	Burgess, Campbell, Osman, Payne and Poulton: <i>Lancet</i> <b>2</b> : 777, 1923 Redisch and Block: <i>Endokrinologie</i> <b>1</b> : 241, 1928
Gelatin and insulin	Uncertain action	Lange and Schoen: <i>Arch. f. exper. Path. u. Pharmacol.</i> <b>113</b> : 92, 1926 Thiel, Ruhnau and Unger: <i>Deutsche med. Wehnschr.</i> <b>60</b> : 975, 1934
Surfen insulin	Comparable in action to protamine zinc insulin	Umber, Störriing and Föllmer: <i>Klin. Wehnschr.</i> <b>17</b> : 443, 1938 Umber, Störriing and Glet: <i>Klin. Wehnschr.</i> <b>17</b> : 190, 1938 Martin: <i>Ztschr. f. d. ges. exper. Med.</i> <b>105</b> : 599, 1939 Holland and Weyer: <i>Zentralbl. f. inn. Med.</i> <b>61</b> : 72, 1940 Schramm: <i>Klin. Wehnschr.</i> <b>19</b> : 470, 1940
Heavy metals, basic compounds and insulin	Retarded action	Jensen: <i>Insulin: Its Chemistry and Physiology</i> , New York, Oxford University Press, 1938, p. 101
Pectin and insulin	Uncertain action	Wuhrmann: <i>Schweiz. med. Wehnschr.</i> <b>69</b> : 1275, 1939
Protein Combinations		
Protamine insulin	Standard in clinical practice	Hagedorn, Jensen, Krarup and Wodstrup: <i>J. A. M. A.</i> <b>106</b> : 177 (Jan. 18) 1936
Acid protamine insulin	Maximum effect in 8 to 10 hours but inconsistent response	Warvel <sup>26</sup> Bailey and Marble <sup>27</sup>
Protamine insulin pellets	Duration of effect 44 to 100 hours	Mark and Biskind: <i>Endocrinology</i> <b>26</b> : 444, 1940
Histone insulin	Action comparable with that of protamine insulin	Bischoff <sup>24a</sup> Gray, Bischoff and Sansum <sup>24b</sup> Bailey and Marble <sup>27</sup> Barnes, Cuttle and Duncan: <i>J. Pharmacol. &amp; Exper. Therap.</i> <b>72</b> : 331, 1941
Globin insulin	Action intermediate between that of soluble and of protamine insulin	Reiner, Searle and Lang <sup>25a</sup> Bauman <sup>25b</sup> Marks <sup>25c</sup> Andrews and Groat: <i>New York State J. Med.</i> <b>40</b> : 913, 1940 Duncan and Barnes <sup>25d</sup> Bailey and Marble <sup>27</sup>
Arginine insulin	Similar in action to protamine insulin	Vartiainen and Bastman: <i>Acta med. Scandinav.</i> <b>98</b> : 318, 1939

TABLE 1.—*Insulin Combinations with Sustained Effects—Continued*

Compound	Comment	Author
Mixtures with Vasoconstrictors		
Extract of posterior pituitary and insulin (deposulin)	Delayed but inconsistent effect	Zirwer: <i>Klin. Wehnschr.</i> <b>16</b> :1121, 1937 Martin: <i>Ztschr. f. d. ges. exper. Med.</i> <b>105</b> : 599, 1939 Holland and Weyer: <i>Zentralbl. f. inn. Med.</i> <b>61</b> :72, 1940 Schweers: <i>Klin. Wehnschr.</i> <b>16</b> :392, 1937 Taeger and Danish: <i>Klin. Wehnschr.</i> <b>16</b> :1639, 1937 Beckmann and Weitzsäcker: <i>Klin. Wehnschr.</i> <b>17</b> :1321, 1938
Epinephrine and insulin	.....	Beckmann and Weitzsäcker: <i>Klin. Wehnschr.</i> <b>17</b> :1321, 1938
Inorganic Modifications		
Ferric chloride and insulin	Augmentation of response	Maxwell and Bischoff: <i>Am. J. Physiol.</i> <b>112</b> : 172, 1935
Zinc and regular insulin or protamine insulin	Prolongation of action of insulin and of protamine insulin	Scott and Fisher <sup>22a</sup> Kerr, Best, Campbell and Fletcher <sup>23b</sup> Rabinowitch, Foster, Fowler and Corcoran <sup>23c</sup>
Tannic acid and insulin	Local reactions	Gray: <i>Endocrinology</i> <b>20</b> :461, 1936
New fraction of pancreas extract with added magnesium chloride (nativ-insulin-depot)	.....	Umber, Störing and Engelmann: <i>Klin. Wehnschr.</i> <b>18</b> :837, 1939 Beckmann and Weitzsäcker: <i>Med. Klin.</i> <b>36</b> : 376, 1940
Alum-precipitated insulin	Peak effect in 8 to 12 hours	Rosenthal, Fialka and Kamlet: <i>Am. J. M. Sc.</i> <b>198</b> :98, 1939
Miscellaneous Combinations		
Safranin and insulin	Prolonged action	Jacobs and Ricketts: <i>Proc. Soc. Exper. Biol. &amp; Med.</i> <b>35</b> :473, 1936
Methenamine and insulin	Clear mixture which precipitates on injection; intermediate effect	Feinblatt: <i>J. Lab. &amp; Clin. Med.</i> <b>24</b> :337, 1939 Alpert: <i>Arch. Pediat.</i> <b>56</b> :647, 1939 Feinblatt, Ferguson and Alpert: <i>Endocrinology</i> <b>26</b> :437, 1940
A protein-free substance and insulin (neoinsulin)	Comparable in action to protamine zinc insulin	Lasch: <i>Deutsche med. Wehnschr.</i> <b>65</b> :1154, 1940
Chloroform-precipitated insulin	Similar in action to protamine zinc insulin	Johlin: <i>Endocrinology</i> <b>29</b> :574, 1941

recent comparative study by Bailey and Marble <sup>27</sup> adequately described the detail of their action. Histone zinc insulin approximates in action that of protamine zinc insulin. The action of globin (zinc) insulin, a soluble preparation, reaches its point of maximum intensity six to twelve hours after injection and wanes appreciably within twenty-four hours. Thus, there is usually no need to supplement its action to control the day feeding periods, and it is less likely to cause nocturnal insulin shock. In these respects it is comparable to some of the mixtures to be described

27. Bailey, C. C., and Marble, A.: Histone Zinc Insulin, Globin (Zinc) Insulin and Clear Protamine Zinc Insulin: A Comparative Study of Their Action, *J. A. M. A.* **118**:683-690 (Feb. 28) 1942.



later. It appears to be the most promising of all other insulins with intermediate effects.

Acid protamine zinc insulin, a soluble preparation derived from ordinary protamine zinc insulin by acidification to a  $p_H$  of about 3.3, possesses an intermediate action similar to that described for globin insulin. However, according to Bailey and Marble, its action is quantitatively inconsistent from dose to dose, possibly because it owes its intermediate effect to partial reprecipitation of protamine zinc insulin by tissue fluids after injection, resulting in variable rates of absorption of uncertain soluble and insoluble fractions.<sup>28</sup> Its action, like that of globin insulin, cannot be varied to suit individual requirements in treatment, an advantage which is inherent in the mixtures to be reported.

#### DETAILED INVESTIGATION OF THE ACTION OF MIXTURES

The need for a preparation which might combine the advantages and eliminate the disadvantages of both standard insulins is amply demonstrated by previous work with mixtures and the extensive search for other suitable insulin combinations. None of them has gained widespread popularity in practice, possibly because none fulfils requirements which are exacting or possibly because simplicity in the treatment of diabetes is highly desirable.<sup>27</sup>

Yet in the treatment of severe diabetes requiring multiple injections there is real need for a preparation with an action intermediate between that of soluble insulin and that of protamine zinc insulin. Hence, the action of mixtures was investigated by means of a method which shows accurately various changes in promptness, intensity and duration of hypoglycemic effects. The results show that (1) regular insulin in sufficient quantity added to protamine zinc insulin is reflected by increasing promptness and intensity of the sugar-reducing response; (2) the response depends on the proportion of insulin added, but only beyond a certain limit; (3) such mixtures are relatively stable, and (4) the response is uniform in a given patient and therefore predictable within the limits of error involved in any form of insulin therapy. A suitable mixture of the two standard insulins can be more efficient for routine use in the treatment of diabetes than either of the elements of which it is composed, as well as more simple and more consistent in response than both injected separately. Multiple injections of soluble and of insoluble insulin may be avoided. These inferences appear to be justified by the responses of constant glycosuria and hyperglycemia in test patients to single doses of various mixtures of the two insulins.

28. Marble, A.: Personal communication to the authors.

## METHOD AND MATERIAL

*Subjects.*—Three carefully selected patients with diabetes mellitus lived quietly in the hospital as test subjects. They were 66, 62 and 56 years old; 2 were women, and all were cooperative, emotionally stable, in normal nutrition and free from acute complications. None had used insulin routinely, and none had shown rapid change in severity of diabetes prior to the tests. Glycosuria and hyperglycemia of moderate and constant degree resulted from the diets outlined in this section; ketonuria and signs of dehydration were absent. These factors are important in well controlled experiments of this nature because all of them are capable of varying the quantitative results and hence affecting their interpretations.

*Food Intake.*—All subjects were fed every four hours, day and night, throughout the experimental periods. On the average their daily weighed intake was carbohydrate 240 Gm., protein 90 Gm. and fat 100 Gm., divided into six equally spaced four hour feedings of almost identical foods and food values. In all cases the measured glycosuria and hyperglycemia were permitted to become constant on each diet for several days before a dose of the insulin to be tested was given.

The amount of blood sugar and urinary sugar showed a uniform tendency to decrease during the afternoon and to increase during the night. These diurnal changes did not affect the twenty-four hour values. They are reflected in the minor fluctuations in the curves to be shown; they do not obscure the major results due to insulin, and they were partially corrected by slight increases in the noon, afternoon and early evening feedings over those of the night and early morning.

In each patient during the two or three months of observation under the conditions just outlined there was a gradual improvement in "tolerance" for ingested food, which resulted in a tendency for the sugar levels to fail to return to their former heights after insulin was given. On this account, the value of the diet was increased slightly on occasion in order to force the sugar to resume its former control levels. Whenever such an increase was made, several days of new control values comparable to those shown previously were obtained before new tests were conducted.

*Insulin.*—Ordinary insulin and protamine zinc insulin were used consistently.<sup>29</sup> One patient (fig. 2) received these two insulins and their mixtures in the U-40 strength only. The other 2 patients received U-80 insulin only. In some instances the two insulins were freshly mixed in the syringe at the time of injection; in others they were mixed in the ampule under sterile precautions and allowed to stand at room or at ice box temperature. No decided variation in effect could be observed with mixtures standing as long as forty-seven days at room temperature.

All injections were made subcutaneously before the 8 a. m. or the 12 noon feeding. All traces of insulin effect from the previous injection were allowed to disappear before a subsequent injection was made, a process usually requiring three to four days.

*Blood and Urinary Sugar.*—Blood was drawn from a vein immediately before a four hour feeding and analyzed by the method of Folin and Wu. The urine of the first patient was collected in four hour specimens after each meal (figs. 1 and 2) and that of the other 2 patients in twelve hour specimens from 8 a. m. to 8 p. m. and 8 p. m. to 8 a. m. (figs. 3 and 4). Urine was analyzed for sugar by the method of Folin and Berglund.

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29. Dr. F. B. Peck and Eli Lilly and Company furnished both types of insulin.

## RESULTS

*Control Values Without Insulin.*—Without insulin the concentration of sugar in the blood and the amount in the urine were fairly constant at the levels of about 250 to 300 mg. per hundred cubic centimeters of blood and 10 to 20 Gm. per twelve hours in the urine (or 2 to 8 Gm. per four hours). These levels were uniform for all 3 patients (tables 2, 3 and 4 and figs. 2 A, 3 A and 4 A). Since the diets prescribed were of the same order of magnitude in all cases, this uniformity indicates comparable severity of diabetes in all 3 patients, suggested further by their consistent responses to similar doses of insulin. Thus the results are peculiarly comparable, not only from dose to dose in the same patient but from patient to patient with the same dose.

As a side issue it is of interest to note the normal diurnal variations in observed levels of sugar in the blood and in the urine without insulin. Invariably, sugar tended to diminish during the day, reaching its lowest

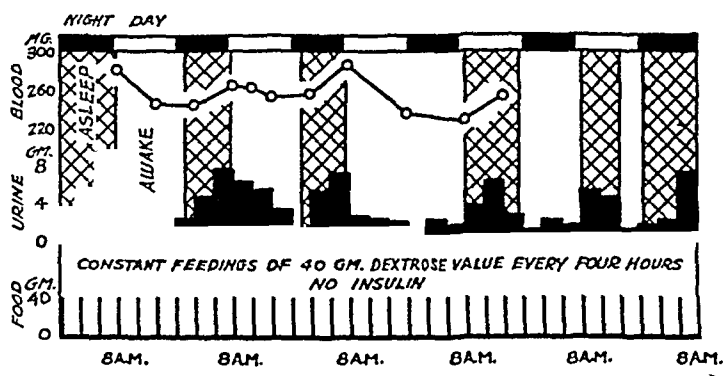


Fig. 1 (patient 1).—Diurnal variations in the levels of blood sugar and urinary sugar despite four hour feedings of constant value. Note the increases during sleep and the decreases during activity, even though the patient slept during the day and was awake at night. No insulin was given.

levels in the late afternoon, followed by increasing levels during the night, which reached their peaks, as a rule, in the early morning hours. This behavior is illustrated typically in the first patient (fig. 1), who after four hour meals of comparable value excreted as little as 2 Gm. of sugar per four hours in the afternoon and as much as 9 Gm. per four hours between 4 and 8 a. m. The concentrations of blood sugar varied in the same directions but to a smaller degree.

On the assumption that these fluctuations, the exact reverse of the well known diurnal variations in body temperature and total metabolism, are normal responses to exercise and activity during waking hours and to retardation of metabolic functions during sleep, this patient's hours of sleep and waking were reversed. For several days she was kept

awake at night and allowed to sleep during the day. The peaks and valleys of sugar excretion and of concentration of sugar in the blood were correspondingly reversed, as shown in the latter part of fig. 1. Thus they proved to be related to activity when awake and inactivity when asleep rather than to specific portions of the day. They could not be related to food, since the feedings were constant day and night.

*Comment.*—Similar observations are on record in the German and the Scandinavian literature.<sup>30</sup> They are not well known in this country. These fluctuations undoubtedly affect the behavior of persons with diabetes with and without insulin and should be respected in planning details of diet and insulin control. In our experience they affect the hour by hour performance of sugar metabolism more profoundly than certain details of timing and quantity of food and insulin which are often stressed in discussions of rules of treatment.

This tendency toward reduction of sugar during the day and increase at night may also affect the responses of normal and of diabetic subjects to standard dextrose tolerance tests. Since such tests are usually performed in the morning, recovery from hyperglycemia may depend as much on a natural tendency for sugar to diminish with activity during the day as to stimulation of insulinogenic function by ingested dextrose. This would be particularly true of the Exton-Rose two dose test.<sup>31</sup>

Commonly accepted interpretations of the Staub-Traugott,<sup>32</sup> or Hamman-Hirschman,<sup>33</sup> phenomenon might be subject to revision by a consideration of the facts just outlined. This phenomenon consists of successive lower hyperglycemic responses to repeated identical doses of ingested dextrose. It is considered to demonstrate an increased capacity to utilize sugar resulting from stimulation of the pancreatic islands by previous doses.<sup>34</sup> Our observations confirm this behavior during the

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day, but since repeated identical feedings during the sleeping hours lead to the opposite, a tendency for sugar to increase, it seems possible that the Staub-Traugott phenomenon is due to a diurnal variation in sugar utilization which occurs as a result of physical activity rather than to stimulation of insulinogenic function by ingested carbohydrate, as commonly supposed. Otherwise, it would also occur during hours of sleep.

TABLE 2.—Effect on the Concentrations of Blood Sugar and Urinary Sugar of Forty Unit and Eighty Unit Doses of U-40 Insulins and Insulin Mixtures \*

Hour	No Insulin		Protamine Zinc Insulin		33% PZI 67% I †		25% PZI 75% I †		20% PZI 80% I		Regular Insulin	
	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Gm./12 Hr.	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Gm./4 Hr.	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Gm./4 Hr.	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Gm./4 Hr.	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Gm./4 Hr.	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Gm./4 Hr.
8 a.m.....	290	...	285	...	281	...	242	...	247	...	251	...
4 p.m.....	...	...	...	...	...	...	...	...	...	...	245	...
8 p.m.....	...	13.3	...	...	...	...	...	...	...	...	...	...
12 midnight....	...	...	...	...	...	...	...	...	...	...	245	...
4 a.m.....	...	...	...	...	...	...	...	...	...	...	...	...
8 a.m.....	281	19.7	272	...	251	...	260	...	260	...	265	...
12 noon.....	...	...	267	5.6	230	4.6	252	4.0	234	4.4	250	4.2
Insulin.....	None		80 units		80 units		80 units		80 units		40 units	
4 p.m.....	245	...	204	4.2	203	3.1	131	1.8	162	2.2	116	0.7
8 p.m.....	...	8.8	194	0.7	179	1.3	89	0.1	77	0.1	170	0.1
12 midnight....	245	...	183	0.1	170	0.2	117	0.1	112	0.1	208	0.9
4 a.m.....	...	...	...	0.1	...	0.2	...	0.1	...	0.1	...	3.4
8 a.m.....	265	15.0	204	1.4	163	0.5	212	2.0	197	0.9	250	7.2
12 noon.....	263	...	185	0.4	180	0.7	237	2.5	225	2.7	263	6.4
4 p.m.....	251	...	...	0.4	185	0.8	198	2.0	218	2.9	251	5.0
8 p.m.....	...	14.7	212	0.5	211	0.6	228	1.7	...	3.9	...	3.3
12 midnight....	256	...	...	1.2	224	0.8	201	1.4	246	2.4	256	1.3
4 a.m.....	...	...	...	4.4	...	3.5	...	2.9	...	6.2	...	5.4
8 a.m.....	288	14.1	281	6.2	249	5.0	237	4.5	236	7.4	288	7.4
12 noon.....	...	...	...	...	...	...	...	...	235	5.3	...	...
8 a.m.....	270	13.8	267	4.7	285	3.5	262	4.1	...	...	272	6.0

\* Patient 1, a 66 year old woman with diabetes of three years' duration. She had not taken insulin previously. Feedings were given every four hours, night and day, with an average dextrose value of 40 Gm.

† Averages for two identical doses. Here and elsewhere in the table PZI refers to protamine zinc insulin and I to regular insulin.

‡ Averages for four identical doses.

These diurnal fluctuations in glycosuria and hyperglycemia in spite of constant feedings were appreciable in all patients studied. They raised the early morning and lowered the afternoon sugar levels slightly. They were obviously not of sufficient magnitude to obscure the major responses to large doses of insulin.

*Responses to Soluble Insulin and to Protamine Zinc Insulin.*—Tables 2, 3 and 4 and figures 2 F, 3 F and 4 D show typical sugar-reducing effects of 40, 80 and 80 unit doses, respectively, of ordinary soluble insulin. Familiar peak effects at about four hours after injection

TABLE 3.—*Effect on the Concentrations of Blood Sugar and Urinary Sugar of Eighty Unit Doses of U-80 Insulins and Insulin Mixtures\**

Hour	No Insulin		Protamine Zinc Insulin		50% PZI 50% I †		33% PZI 67% I †		25% PZI 75% I		Regular Insulin	
	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Gm./12 Hr.	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Gm./12 Hr.	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Gm./12 Hr.	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Gm./12 Hr.	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Gm./12 Hr.	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Gm./12 Hr.
8 a.m.....	...	...	261	...	255	...	282	...	276	...	310	...
4 p.m.....	261	...	...	...	...	...	286	...	...	...	...	...
8 p.m.....	...	8.7	...	9.2	239	15.0	...	19.1	...	17.8	...	17.9
12 midnight...	305	...	...	...	...	...	301	...	...	...	...	...
8 a.m.....	310	16.5	284	9.7	250	7.3	292	12.5	276	9.5	284	19.3
Insulin.....	None		80 units		80 units		80 units		80 units		80 units	
12 noon.....	...	...	...	...	253	...	242	...	162	...	61	...
4 p.m.....	...	...	248	...	204	...	193	...	82	...	132	...
8 p.m.....	...	11.2	247	7.0	183	7.8	161	6.1	83	0.8	245	1.5
12 midnight...	...	...	235	...	149	...	153	...	87	...	230	...
8 a.m.....	302	11.5	206	2.3	126	0.5	181	0.2	175	0.3	292	7.0
4 p.m.....	...	...	187	...	183	...	215	...	235	...	263	...
8 p.m.....	...	9.4	...	0.5	...	2.9	...	3.9	...	5.3	...	...
12 midnight...	288	...	217	...	219	...	224	...	230	...	...	...
8 a.m.....	286	14.8	253	1.4	242	10.1	252	5.1	250	5.1	250	21.0
8 p.m.....	315	14.7	242	2.8	235	...	249	9.3	230	...	315	...
8 a.m.....	312	12.0	274	4.0	247	11.5	250	4.3	229	8.2	294	21.5
8 p.m.....	301	12.3	...	5.0	231	...	...	11.0	...	...	...	...
8 a.m.....	312	10.4	298	4.0	244	10.3	269	7.4	258	7.7	...	...

\* Patient 2, a 62 year old woman with diabetes of one year's duration. She had not taken insulin previously. Feedings were given every four hours, night and day, with an average dextrose value of 45 Gm.

† Throughout the table PZI refers to protamine zinc insulin and I to regular insulin.

‡ Averages for four identical doses.

TABLE 4.—*Effect on the Concentrations of Blood Sugar and Urinary Sugar of Eighty Unit Doses of U-80 Insulins and an Insulin Mixture\**

Hour	No Insulin		Protamine Zinc Insulin		25% PZI 75% I †		Regular Insulin ‡	
	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Gm./12 Hr.	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Gm./12 Hr.	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Gm./12 Hr.	Blood Sugar, Mg./100 Cc.	Urinary Sugar, Gm./12 Hr.
8 a.m. ....	266	...	238	...	272	...	280	...
8 p.m. ....	...	...	248	19.2	227	13.8	256	18.6
8 a.m. ....	274	16.7	242	15.7	277	18.5	270	16.4
Insulin.....	None		80 units		80 units		80 units	
12 noon.....	...	...	213	...	71	...	63	...
4 p.m.....	...	...	196	...	75	...	123	...
8 p.m.....	...	...	178	11.2	85	3.1	236	1.9
12 midnight...	...	...	190	...	90	...	228	...
8 a.m.....	283	15.8	206	7.0	157	0.3	277	13.1
4 p.m.....	...	...	184	...	205	...	252	...
8 p.m.....	256	...	...	5.5	...	3.3	242	18.1
12 midnight...	...	...	205	...	213	...	...	...
8 a.m.....	286	17.6	200	6.3	256	11.1	275	17.1
8 p.m.....	256	...	248	15.0	...	9.4	216	17.2
8 a.m.....	286	17.8	242	19.0	269	11.2	255	13.3

\* Patient 3, a 56 year old man with diabetes of 12 years' duration. He had not taken insulin previously. Feedings were given every four hours, night and day, with an average dextrose value of 56 Gm.

† Averages for two identical doses. PZI refers to protamine zinc insulin and I to regular insulin.

and return to control levels within twenty-four hours are apparent, accompanied by substantial reduction of glycosuria for twelve to twenty-four hours.

Figures 2 *B*, 3 *B* and 4 *B* and tables 2, 3 and 4 illustrate typical responses to 80 unit doses of protamine zinc insulin, with signs of maximum intensity at twenty-four to thirty-two hours after administration and associated gradual and prolonged reduction of glycosuria for at least two days.

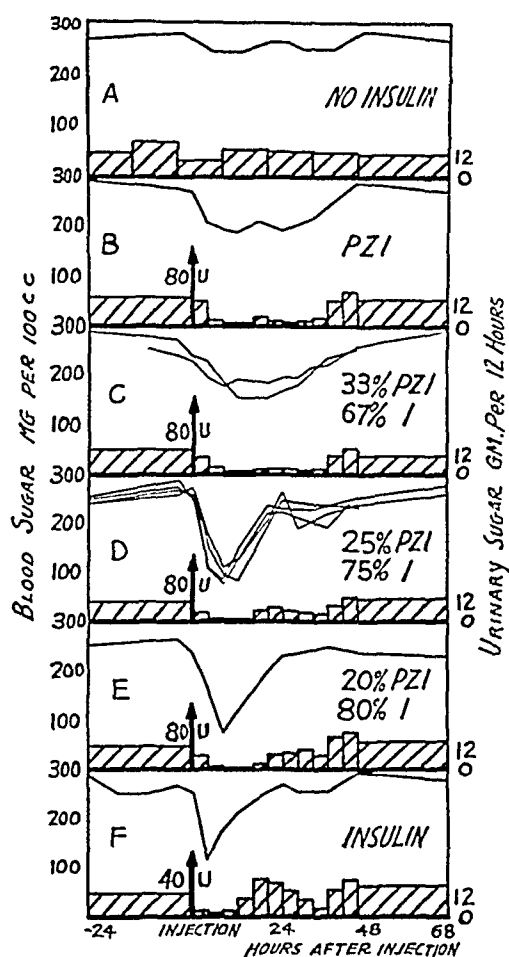


Fig. 2 (patient 1).—A graphic record of the values in table 2. *A*, no insulin was given. *B*, the response to protamine zinc insulin (PZI). *C*, *D* and *E*, intermediate responses to mixtures containing increasing proportions of ordinary insulin (*I*). Superimposed curves represent the responses to repeated identical doses. *F*, the response to ordinary insulin. Contrast this with the response to protamine zinc insulin (*B*).

*Comment.*—Although these data illustrate the pharmacologic reactions to the two standard insulins in doses somewhat larger than those commonly used in routine treatment, their characteristic time relations and comparable intensity and duration of reaction vividly illustrate the

difficulties inherent in treatment with one or both of them in cases of severe diabetes in which large doses are required. The prompt, brief action of ordinary insulin causes violent hypoglycemia and permits heavy glycosuria and acidosis unless it is given at frequent intervals. The weak, sustained action of protamine zinc insulin permits glycosuria after meals and tends to cause nocturnal hypoglycemia during fasting.<sup>35</sup> Hence a single insulin with an intermediate action is highly desirable.

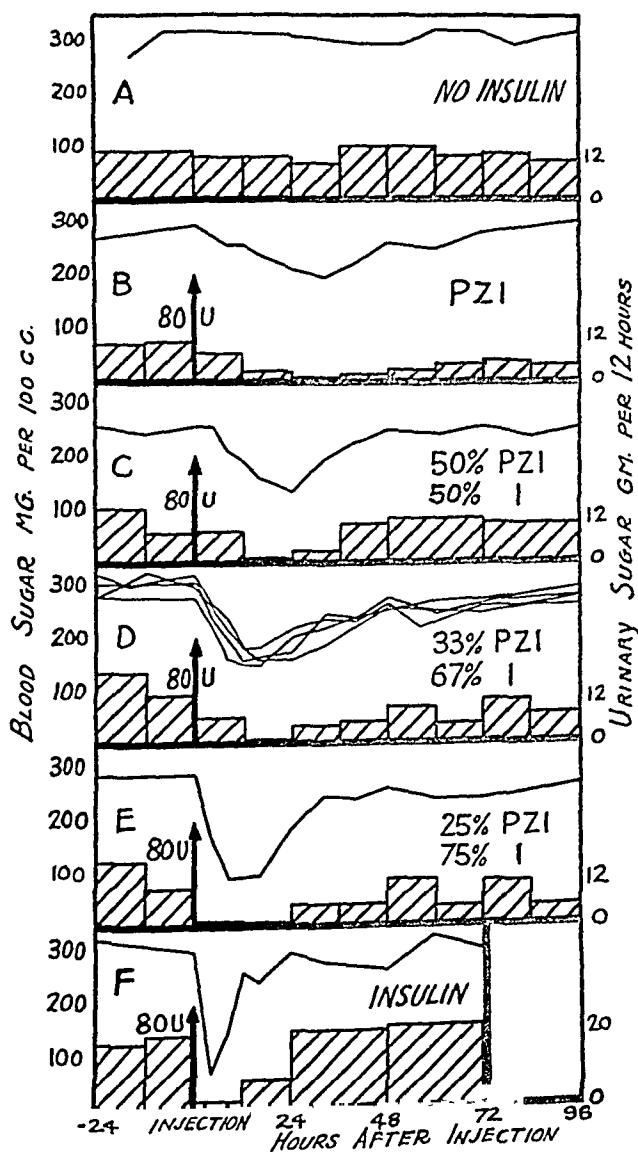


Fig. 3 (patient 2).—A graphic record of the values in table 3. *A*, no insulin was given. *B*, the response to protamine zinc insulin (PZI). *C*, *D* and *E*, intermediate responses to mixtures containing increasing proportions of ordinary insulin (*I*). Note the similarity between the curves in *C* and *B*. The superimposed curves in *D* represent responses to repeated identical doses, two of which were mixed several weeks before injection. *F*, the response to ordinary insulin. Contrast this with the response to protamine zinc insulin (*B*).

35. Footnotes 4 and 5.



*Response to Mixtures.*—The comparative effects of various mixtures of the two insulins are graphically illustrated in figures 2 *C, D* and *E*; 3 *C, D* and *E*, and 4 *C*. Tables 2, 3 and 4 present the actual values obtained. In effect a mixture containing equal proportions of the two insulins (fig. 3 *C*) is barely distinguishable from protamine zinc insulin; a mixture containing four parts soluble insulin and one part protamine zinc insulin (fig. 2 *E*) resembles ordinary insulin, but the action of the latter mixture reaches its peak about twice as late and recedes more slowly. Intermediate mixtures containing two and three parts of soluble insulin to one part protamine zinc insulin show inter-

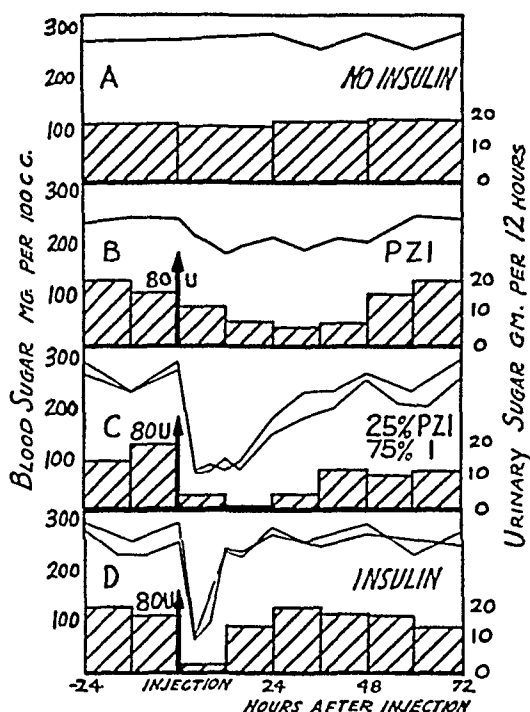


Fig. 4 (patient 3).—A graphic record of the values in table 4. *A*, no insulin was given. *B*, the response to protamine zinc insulin (PZI). *C*, intermediate responses to a 3:1 mixture of regular insulin (*I*) and protamine zinc insulin after duplicate identical doses. *D*, the response to ordinary insulin. Contrast this with the response to protamine zinc insulin (*B*).

mediate actions (figs. 2 *C, 2 D, 3 D, 3 E* and 4 *C*). With characteristic peak effects at eight to sixteen hours, contrasting with four hours for soluble insulin and twenty-four hours or later with protamine zinc insulin; intensity intermediate between the other two, and definite waning effects at twenty-four hours, these mixtures clearly possess pharmacologic properties intermediate between those of insulin and of protamine zinc insulin. In these respects the mixtures all run in series from one extreme to the other.

The characteristic reactions of identical doses of these insulins and their mixtures in various proportions appeared uniform enough in the 3 test subjects to justify a composite graph and diagrammatic deduction as to their actions. Figure 5 *A* shows four mean curves obtained by computing averages for all tests with 80 unit doses of the two insulins and two of their mixtures. In figure 5 *B* these curves are smoothed out in diagrammatic fashion. The smoothing process is intended arbitrarily to eliminate or discount obvious irregularities caused by diurnal variations due to activity and sleep rather than to insulin.

Composite curves obtained in this manner show clearly the familiar blood sugar-reducing effects of large doses of regular insulin and of

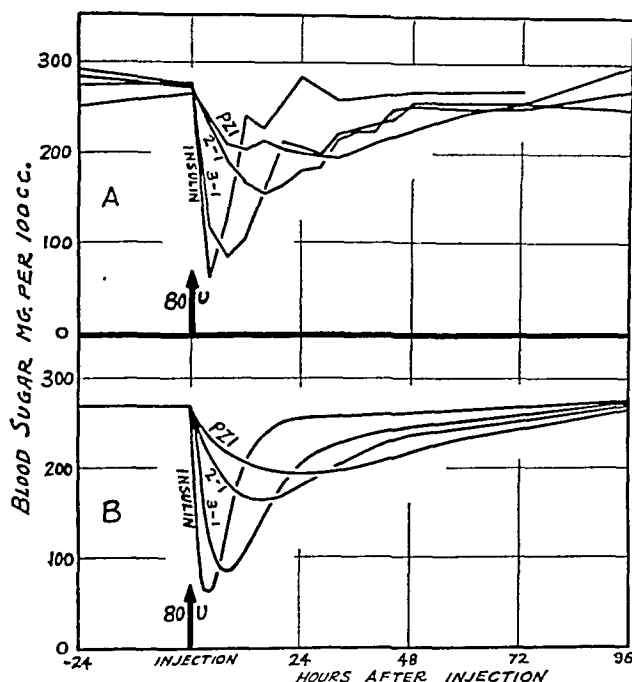


Fig. 5.—*A*, average blood sugar curves for all identical doses of similar insulins or insulin mixtures in all patients (*PZI*, protamine zinc insulin; *2-1*, a mixture containing two parts regular insulin to one part protamine zinc insulin, and *3-1*, a mixture containing three parts regular insulin to 1 part protamine zinc insulin). *B*, diagrammatic representation of the average curves shown in *A*, arbitrarily smoothed to discount minor irregularities considered not to be due to insulin.

protamine zinc insulin. Their characteristic forms establish confidence in the accuracy of the method of study. The curves illustrating the effects of the two most frequently studied mixtures are clearly intermediate between those of the two standard types of insulin. They show increasing promptness and intensity of action associated with more rapid waning as excesses of soluble insulin are added to the mixtures. Other single curves not included in the composite group fit into this scheme. All of them confirm the observations of Ulrich that little acceleration of

effect is obtained until at least as much regular insulin as protamine zinc insulin is used in the mixtures.<sup>19</sup>

Therefore, it is possible to conclude that mixtures of ordinary insulin and protamine zinc insulin in the U-40 or U-80 strengths used in this study can be combined empirically in mixtures containing at least as much of the former as the latter, with increasing acceleration and diminishing duration of effect in a consistent and graduated series as more soluble insulin is added.

*Comment.*—The intermediate modifications containing 67 and 75 per cent soluble insulin consistently show peaks of sugar-reducing activity eight to sixteen hours after injection, which would correspond to late afternoon and evening if daily morning injections were given. The effects tend to wane within twenty-four hours after injection, which would correspond to the night hours of fasting with daily morning injections. Both features appear desirable from the standpoint of clinical usefulness.

However, when one considers the possible clinical use of such modifications, it must be remembered that the promptness, intensity and duration of effect described for them occur under conditions which are different from those existing in practice. First, the doses illustrated are larger than those generally used daily by diabetic patients. Second, in these experiments the blood sugar and urinary sugar decrease from levels much higher than those existing in patients with well controlled diabetes at the time of insulin injection. Third, the subjects reported ate generous carbohydrate meals every four hours, even during the night. Finally, the reactions of the 3 test subjects described may not be average for all diabetic patients. Hence, clinical applications of these actions of specific mixtures must be made with extreme caution and with full consciousness of the different conditions in routine treatment from those reported here. Our own experience in this respect is reported in the following section.

Questions concerning the consistency of repeated injections of the same preparations are answered by figures 2 C, 2 D, 3 D and 4 C. These curves show the blood sugar responses to two and to four identical doses of the same mixture in the same subject. The response appears to be fairly dependable and predictable, as noted by Ulrich, using other methods. Complete uniformity of response would be a desirable property of any relatively slow-acting insulin. Certainly one of the chief disadvantages of protamine zinc insulin is its tendency to permit undulating variations in control from day to day.

The modifications described apparently are stable for weeks, at least. In figure 3 D two of the four superimposed blood sugar curves followed

injection of mixtures which were freshly prepared. The other two followed identical doses of similar mixtures prepared in an ampule and allowed to stand at room temperature for thirty and forty-seven days.

#### NATURE OF THE MODIFIED INSULIN

In addition to precipitated insulin, water and preservative, protamine zinc insulin contains protamine (much of it uncombined), zinc and dibasic sodium acid phosphate. Of these last-named three ingredients, ordinary insulin contains only zinc in about one-tenth the quantity present in protamine zinc insulin. Therefore, on an empiric basis mixtures like those reported should contain less than half the quantity of all three substances in proportion to their insulin content. Which of these ingredients in reduced concentration is responsible for the accelerated action is not known. Theoretically, less of any one of them would be capable of accelerating the slow action of protamine zinc insulin.

The addition of zinc certainly prolongs the action of protamine insulin. How much less than 0.2 mg. of zinc per hundred units would be required to modify the effect is not known. There is also evidence that increased acidity and reduced protamine both modify the action of protamine zinc insulin in the direction shown by the mixtures. We have reason to believe that reduced protamine is the major cause for the accelerated action but that increased acidity and less zinc are also capable of modifying the action in the same manner. Which of the two last-named factors is more important is speculative.

As noted by Ulrich, the modified insulin action exhibited by these mixtures is probably not due to soluble insulin in them.<sup>19</sup> We have confirmed his observation that the supernatant liquid from a centrifuged mixture containing three parts soluble insulin and one part protamine zinc insulin is essentially free from insulin effect. Therefore, the insulin in the mixture must be in precipitated form, possibly adsorbed on the protamine zinc insulin precipitate or possibly in the form of a more freely soluble protamine insulinate than that existing in the presence of more protamine and in the more alkaline suspension. Further studies on the nature of the modified insulin are in progress and will be reported.

#### THERAPEUTIC EXPERIENCE

Practical application of the mixtures just described has been deliberately restricted to careful observation of a few selected patients. Twelve patients, most of them with severe diabetes of the juvenile type, have used mixtures containing 60 to 75 per cent ordinary insulin and 40 to 25 per cent protamine zinc insulin in single daily doses (in 1 instance twice daily) for periods up to six months. Nine patients had used

protamine zinc insulin with supplementary injections of soluble insulin previously, causing irregularly imperfect control. They had been unable to avoid waves of heavy glycosuria under the best possible conditions with weighed diets and separate injections. Hypoglycemic symptoms had been frequent and unpredictable.

In 8 of these 9 patients the severe diabetes is under decidedly better control with a single daily dose of a 2 to 1 or 3 to 1 mixture than with a single daily dose of protamine zinc insulin supplemented by one or two small daily doses of soluble insulin. One patient reverted to separate injections after a three week trial on a 3 to 1 mixture. In this instance an infection of the respiratory tract during the period of trial probably vitiated the results. In the other 3 patients the diabetes was capable of good control with protamine zinc insulin alone; the control is fully as good with a mixture of two or three parts soluble insulin and one part protamine zinc insulin.

The chief difficulty encountered so far has been a tendency to hypoglycemia at the hour when it would be anticipated, i. e., in the late afternoon, at the point of coincidence of the greatest activity of the day with the peak of the insulin action. In some instances reduction of the total dose or increases in the noon meal and insertion of a midafternoon feeding have been sufficient to prevent hypoglycemic symptoms without increases in glycosuria elsewhere. In other cases mixtures containing less soluble insulin may be preferable. They have not yet been tried. In practically all cases a substantial reduction in dose has been necessary when mixtures were used.

#### SUMMARY

Responses of constant hyperglycemia and glycosuria to single doses of insulin, protamine zinc insulin or simple mixtures of the two in various proportions justify the following conclusions:

1. Suitable mixtures of the two standard insulins may be prepared which show any desired intermediate action between the two in promptness, intensity and duration of effect.
2. Such intermediate effects gain intensity and promptness at the expense of prolongation of action. The converse is also true.
3. Intermediate effects which are decisive cannot be obtained with simple mixtures of the two insulins until as much soluble insulin as protamine zinc insulin is used in them.
4. Probably mixtures containing more regular insulin than protamine zinc insulin, possibly two or three times as much, are most suitable for daily use in the treatment of severe diabetes.
5. Such mixtures owe their intermediate effects to reduction in the amount of protamine, zinc or alkaline buffer. There is evidence to

indicate that insulin in a different physical or chemical form is responsible for the modified action rather than composite effects from simple fractions of soluble insulin and insoluble protamine zinc insulin.

6. Results of treatment with these modifications suggest that better control of severe diabetes mellitus may be obtained with single daily doses of one of them than with protamine zinc insulin or unmodified insulin given alone or both administered simultaneously in separate doses. Multiple injections may be avoided and dosage reduced because of greater efficiency.

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# DISTRIBUTION OF SPECIFIC TYPES OF HEMOLYTIC STREPTOCOCCI IN EIGHT HUNDRED AND NINETEEN CASES OF INFECTION

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In two previous papers by two of us (L. A. R. and C. S. K.) and an associate<sup>1</sup> it was pointed out that hemolytic streptococci of groups A, B and C can be readily distinguished by the specific precipitin method of Lancefield<sup>2</sup> and that they also give distinctive types of hemolysis in standard poured blood agar plates.<sup>1a</sup> Group A hemolytic streptococci are made up of a number of specific types, which may be distinguished by appropriate serologic methods.<sup>3</sup> For this purpose two procedures have been used, (1) the slide agglutination method of Griffith<sup>4</sup> and (2) the precipitin method of Lancefield.<sup>2</sup> Of the two, the slide agglutination method has had wider use. Most of the reports concerning the distribution of specific types of hemolytic streptococci in human disease have

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been made from England<sup>5</sup> and Australia,<sup>6</sup> but a few have appeared from Japan,<sup>7</sup> Germany<sup>8</sup> and the United States.<sup>9</sup> In 1938 and 1939 we were able to study 819 strains of group A hemolytic streptococci by the slide

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8. Gundel, M., and Wüstenberg, J.: Untersuchungen über hämolytische Streptokokken und die Bedeutung ihrer Typendifferenzierung, *Zentralbl. f. Bakt. (Abt. 1)* **138**:325, 1937.

9. (a) Bradley, W. H.: Epidemiology of Streptococcal Infections, *Guy's Hosp. Rep.* **87**:372, 1937. (b) Pauli, R. G., and Coburn, A. F.: Studies on Serological Typing of Streptococcus Haemolyticus, *J. Exper. Med.* **65**:595, 1937. (c) Bailey, J. H.: Types of Hemolytic Streptococci Found in Scarlet Fever Patients and in Throats of Grammar-School Children, *Am. J. Hyg.* **29**:107, 1939. (d) Diddle, A. W.; Trussell, R. E., and Plass, E. D.: Scarlet Fever in Obstetrics: A Report of an Epidemic, *Am. J. Obst. & Gynec.* **39**:608, 1940. (e) Kuttner, A. G., and Krumwiede, E.: Observations on the Effect of Streptococcal Upper Respiratory Infections on Rheumatic Children: A Three-Year Study, *J. Clin. Investigation* **20**:273, 1941. (f) Coburn, A. F., and O'Connell, S.: Advances in the Serological Typing of Streptococcus Haemolyticus, *Proc. Soc. Exper. Biol. & Med.* **40**:645, 1939. (g) Swift, H. F.; Lancefield, R. C., and Goodner, K.: Serological Classification of Haemolytic Streptococci in Relation to Epidemiologic Problems, *Am. J. M. Sc.* **190**:445, 1935.



agglutination technic. The rabbit serum for this investigation was made by using subcultures of the original Griffith strains. The purpose of the study was to determine the types of streptococci which were prevalent those years and to ascertain whether any information concerning the severity of infection, complications and other features of the infections could be related to specific types.

#### MATERIAL AND METHOD

Cultures were made of material from various foci of infection in poured blood agar plates, and beta hemolytic streptococci were isolated. They were first identified as to group, according to the microprecipitin method of Brown.<sup>10</sup> Strains which proved to belong in group A were then set up for typing. The slide agglutination method of Griffith<sup>4a</sup> was used. The organisms were grown in various kinds of medium in an attempt to obtain stable and even suspensions. We found that the growth of organisms in trypsin broth was satisfactory for most strains, since the

TABLE 1.—*Foci of Infection from Which Hemolytic Streptococci Were Isolated*

	Number of Strains	Percentage
Throat infections.....	531	64.0
Otitis media and mastoiditis.....	120	14.0
Abscesses (miscellaneous).....	58	7.0
Pneumonia and empyema.....	57	7.0
Bacteremia.....	37	4.7
Erysipelas.....	12	1.6
Meningitis.....	4	0.5
Total.....	819	

suspensions were more likely to be nongranular in this medium. When the cultures were granular, it was not possible to use them for typing. The serums were absorbed, so that cross reactions were eliminated. The sources of the organisms are shown in table 1.

#### DISTRIBUTION OF TYPES OF HEMOLYTIC STREPTOCOCCI IN VARIOUS DISEASES

The distribution of the various types of hemolytic streptococci in different diseases is shown in table 2. Six hundred and thirty-seven, or 79 per cent, of the 819 strains were typed with the serums that were available. The frequency with which we identified these types ranged from 61 to 83 per cent in the various diseases. In the cases of pneumonia and tonsillitis, we identified 61 and 65 per cent of the strains, respectively, whereas in the cases of scarlet fever, otitis media and mastoiditis 83 per cent of the strains were typed. It has been recognized by

10. Brown, J. H.: A Simplified Method for Grouping Hemolytic Streptococci by the Precipitin Reaction, J. A. M. A. **111**:310 (July 23) 1938.

every one who has attempted to identify types of hemolytic streptococci that it is more difficult to type strains which are isolated from persons with puerperal sepsis<sup>11</sup> or the throats of carriers than it is to identify those which are isolated from the throats of patients with scarlet fever. This is probably due to the fact that there are many types other than the ones originally isolated by Griffith which have not been identified and properly classified.

It is seen from table 1 that in cases of otitis media, mastoiditis, pneumonia, abscess and erysipelas which were studied during the same

TABLE 2.—*Distribution of Types of Causative Hemolytic Streptococci in Various Diseases*

Type	Scarlet Fever	Tonsil- litis	Otitis Media and Mas- toiditis	Abscess	Pneu- monia	Em- pyema	Bac- teremia	Ery- sipelas	Men- ingitis	Total
1.....	20	6	13	5	3	..	3	2	..	52
2.....	20	..	3	..	4	..	..	..	..	27
5.....	2	..	..	..	..	..	..	..	..	2
6.....	1	1	1	..	..	..	..	..	..	3
8.....	2	..	3	..	..	..	..	..	..	5
9.....	1	..	..	1	1	..	..	..	..	3
10.....	4	..	..	1	..	..	..	..	..	5
11.....	23	18	15	12	..	..	6	2	..	76
12.....	5	1	8	3	1	2	2	1	1	24
13.....	101	7	16	5	4	3	2	..	..	138
14.....	1	..	..	..	..	..	..	..	..	1
15.....	151	27	25	5	11	6	15	1	1	242
19.....	1	..	..	..	..	..	..	..	..	1
21.....	1	..	..	..	..	..	..	..	..	1
25.....	3	6	10	3	..	..	2	..	..	24
26.....	..	1	..	..	..	..	..	..	..	1
27.....	2	7	4	4	1	..	2	2	..	23
28.....	1	2	1	4	..	..	..	1	1	9
29.....	2	..	..	..	..	..	..	..	..	2
Typing unsuccessful.....	73	41	21	15	16	5	5	3	1	180
Total.....	414	117	120	58	41	16	37	12	4	819
Per cent of total no. of strains typed...	83	65	83	74	61	69	70	75	75	79

period the infections were due to the same types of organism which were causing scarlet fever and tonsillitis. Another fact was noticeable; namely, when one type was most prevalent in patients with scarlet fever, it was also prevailing in those with other infections caused by hemolytic streptococci.

*Scarlet Fever.*—Of the 414 strains isolated from the throats of patients with scarlet fever, we were able to type 83 per cent of the

11. (a) Colebrook, D. C.: The Source of Infection in Puerperal Fever Due to Hemolytic Streptococci, Medical Research Council, Special Report Series, no. 205, London, His Majesty's Stationery Office, 1935. (b) Footnote 5 h and i. (c) Butler and Hill.<sup>6a</sup>

strains, and 75 per cent of them were found to fall into the following five types: 15, 13, 11, 1 and 2. When these results were compared with the typing of strains isolated from patients with tonsillitis, it was found that only 65 per cent of these strains could be typed, but the types which predominated were 15, 11, 13, 1, 25 and 27. There were no instances of tonsillitis due to hemolytic streptococci of type 2.

When the strains isolated from patients with scarlet fever and with tonsillitis were considered together, there were 531 strains and 79 per cent were typed. Seventy per cent of the strains fell into types 15, 13, 11, 1 and 2. The remaining 9 per cent were scattered among the other types. This is shown in table 3.

From these studies it is plain that the number of types responsible either for scarlet fever or for tonsillitis during the period of observation was relatively small, but the distribution of types was different from that reported elsewhere.

TABLE 3.—*Distributions of Types of Hemolytic Streptococci Isolated from Patients with Scarlet Fever and with Tonsillitis*

Type	Total No. of Strains	Percentage
15	178	33.0
13	108	20.0
11	41	7.7
1	26	4.8
2	20	3.9
		<hr/> 69.4

In the studies of the distribution of types of streptococci which cause scarlet fever in England and Scotland<sup>12</sup> it appears that while a large number of types are capable of causing scarlet fever, the commonest are types 1 to 5 inclusive, and they account for at least 60 per cent of all strains isolated. In a single study reported from Germany by Gundel and Wüstenberg<sup>8</sup> the same general distribution was found. In Australia, however, the distribution as reported by various investigators has varied from one community to another.<sup>13</sup> For example, in Sydney types 1, 4, 11 and 17 accounted for most of the streptococci causing scarlet fever. In Adelaide a type not included in Griffith's strains and called "Wade" strain was responsible for 55 of 78 infections, and in Melbourne type 2 predominated. According to a recent report from Scotland, types 1, 2, 4, 8, 11 and 15 predominated.<sup>51</sup> It is almost a universal experience that during an epidemic of scarlet fever one type of hemolytic streptococcus accounts for the majority of cases occurring in a community, and this

12. Footnote 5 *a* through *k*.

13. Footnote 6 *b*, *c* and *d*.

is especially striking when epidemics are studied in institutions. As an epidemic progresses in the same community, one specific type may be replaced by another. De Waal<sup>51</sup> described two epidemics of scarlet fever, occurring at the same time in communities 12 miles (19 kilometers) apart, which were due to different types.

In the United States Bailey<sup>9c</sup> found in 1934 and 1935 that types 2, 3 and 6 were the predominant types causing scarlet fever in Chicago. In New York city Pauli and Coburn<sup>9b</sup> and Coburn and O'Connell<sup>9f</sup> have shown that the predominating types in infections caused by hemolytic streptococci vary from year to year. In the years 1935 and 1936 types 4, 22 and 13 were common, and in 1937 and 1938 type 30 accounted for 35 per cent of the strains isolated and types 13, 15, 25, and 27 accounted for another 25 per cent of strains. They did not encounter one strain of type 10 in four years, although this strain (NY 5) was known to be prevalent for some years in and around New York city. The strains which were isolated in the early fall from cultures of material from the throats of healthy subjects frequently were difficult to type. Recently, Kuttner and Krumwiede<sup>9e</sup> reported their results of a study of pharyngitis caused by hemolytic streptococci in an institution over a three year period. During this time three different strains were isolated during epidemics of such pharyngitis, that is, a different strain every year. The first year it was C51, a group A strain which is not included in the 30 types identified by Griffith; the second year it was a strain of type 4, and the third, a strain of type 27. Other strains isolated at various periods included ones of types 2, 5, 6, 12, 17, 18 and 29.

Our own experience indicates, then, that during any one year the total number of strains which cause disease may be limited. During the period in which we studied the subject the predominating types were 15, 13, 11, 1 and 2, which accounted for 85.4 per cent of all the types identified.

From these various studies concerning the distribution of specific types of hemolytic streptococci which cause scarlet fever in different countries or in different communities of the same country the following facts emerge:

1. Scarlet fever may be caused by a wide variety of specific types of hemolytic streptococci.
2. The predominant types vary from one country to another, from one community to another in the same country and from year to year in the same country or community.
3. During an epidemic in a community, one type usually predominates or two types may thrive simultaneously. This is most noticeable when epidemics occur in schools or institutions.

4. As an epidemic progresses in the same community, one type may be replaced by another, so that the type which may be common at one season may be replaced by another type later.

5. In sporadic cases of scarlet fever the infections are more often due to types which are not concerned with the types causing the epidemic, and there is often a wide scattering.

6. When a relapse occurs in a patient with scarlet fever, it is usually because of infection by a different type of hemolytic streptococcus and because the patient's reaction to the Dick test has failed to become negative as a result of the first attack.

TABLE 4.—*Distribution of Types of Hemolytic Streptococci Causing Otitis Media and Mastoiditis in Patients With and Without Scarlet Fever*

Type	Total No. of Patients With Scarlet Fever	Patients With Otitis Media		Patients With Mastoiditis	
		With Scarlet Fever	Without Scarlet Fever	With Scarlet Fever	Without Scarlet Fever
15.....	151	9	16	0	4
13.....	101	12	4	0	1
11.....	23	1	14	0	10
1.....	20	4	9	0	3
2.....	20	1	2	0	0
12.....	5	2	6	0	3
25.....	3	0	10	0	3
10.....	4	0	0	0	0
5.....	2	0	0	0	0
8.....	2	1	2	0	1
27.....	2	0	4	0	1
29.....	2	0	0	0	0
6.....	1	1	0	0	0
9.....	1	0	0	0	0
14.....	1	0	0	0	0
19.....	1	0	0	0	0
21.....	1	0	0	0	0
28.....	1	0	1	0	1
Unidentified types.....	73	5	16	0	11

The relation of complications to type are discussed in a later section of the paper.

*Otitis Media and Mastoiditis.*—In this group there were 120 patients, 82 with otitis media alone and 38 with associated mastoiditis. That is to say, mastoiditis developed in 31 per cent of the patients with otitis media. Seventy-two per cent of the infections were accounted for by five different specific types: 15, 13, 11, 1 and 25. These were the types which were common in the throats of patients with scarlet fever and with tonsillitis during this period. The relative frequency of the different types causing otitis media and mastoiditis is listed in table 4. Also, in table 4 the relative frequency of otitis media and mastoiditis in patients with and in those without scarlet fever is recorded. The total incidence of otitis media in 414 patients with scarlet fever was 8.9 per cent. Since

the average incidence of otitis media following scarlet fever is about 12.5 per cent,<sup>14</sup> this is not an excessively high complicating rate in our series. When the causative organisms were analyzed for type, types 13, 9, 1 and the unidentified types were the most frequent cause of otitis media following scarlet fever. Types 11 and 15 and unidentified types caused most of the mastoiditis without preceding scarlet fever. Indeed, mastoiditis failed to develop in any of the 36 patients with otitis media following scarlet fever. This may have been due to treatment with sulfanilamide. Many of the patients who had mastoiditis without preceding scarlet fever were admitted to the hospital with well developed mastoiditis.

De Waal<sup>51</sup> reported otorrhea in 80 cases of scarlet fever, and types 4, 1 and 15 were common ones isolated in these cases.

In our patients mastoiditis occurred more often after otitis media without scarlet fever than with this disease. The incidence of this complication of otitis media may be reduced by using sulfanilamide regularly in all cases. Moreover, the occurrence of otitis media as a late complication of scarlet fever may be reduced either by preventing reinfection or by using sulfanilamide during the course of the disease.

*Erysipelas.*—In a previous study by one of us (C. S. K.) with an associate of 22 strains of hemolytic streptococci isolated from patients with erysipelas, it was found that they all belonged to group A and they did not differ from those obtained from patients with other infections.<sup>15</sup> In this study 12 strains were isolated, and 9 of them were typed, including types 1, 11, 12, 27 and 15. It was not surprising to find the same types in patients with erysipelas as were prevalent in persons with infections of the respiratory tract, since the same type of hemolytic streptococcus is frequently present in the nose and throat and in the cutaneous lesion. Indeed, there is good evidence that erysipelas of the face frequently follows infections of the nose and throat or infections of wounds caused by hemolytic streptococci. De Waal<sup>51</sup> has recently reported his results of typing hemolytic streptococci isolated in 40 cases of erysipelas; he found types 1, 2, 3, 4, 7, 25, 28 and 30 most often. It was of interest that he found type 7 in 6 cases, since this type belongs to group C Lancefield, and in our own experience we failed to isolate any organisms of this type from infections in human beings. A point of some interest was the fact that erysipelas in young persons, i. e., ones under 20 years

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14. Abrams, J. I., and Friedman, S.: The Problem of Otitis Media and Mastoiditis in Scarlet Fever, *New England J. Med.* **209**:494, 1933. Wesselhoeft, C.: Factors Influencing the Incidence and Course of Otitis Media in Scarlet Fever, *Ann. Int. Med.* **12**:1473, 1939.

15. Keefer, C. S., and Spink, W. W.: Studies of Hemolytic Streptococcal Infection: III. The Characteristics of the Hemolytic Streptococci Isolated from Patients with Erysipelas, *J. Clin. Investigation* **16**:155, 1937.

of age, was associated with the types of hemolytic streptococci which were prevalent in the epidemic forms of this disease (types 1 to 4), whereas in the older patients the nonepidemic types prevailed. Also, in 1 case of recurrent erysipelas, the same type (type 7) was isolated on two different occasions. All of our patients with erysipelas recovered except 1 who had associated heart disease.

*Pneumonia and Empyema Caused by Hemolytic Streptococci.*—Forty-one patients had pneumonia and 16 had empyema caused by hemolytic streptococci. In the 41 patients with pneumonia, we were able to type 61 per cent of the causative strains of streptococci. In order of frequency, the types were 15, 13, 2, 1, 12, 9 and 27. The types which were associated with empyema were 15, 12 and 13. There was no correlation between the type of organism and the outcome, although the group was too small to draw definite conclusions. Empyema was more common in the patients under 30 years of age, and the fatality rate was correlated with age and the presence of bacteremia rather than with the type of infecting organism. That is, patients over 50 years of age and those with bacteremia have a poor prognosis. Those under 40 years of age without bacteremia frequently survive. It is well to point out that the organisms responsible for pneumonia were the same as those which were causing other infections. A full account of the cases of these patients has been published elsewhere,<sup>16</sup> but in order to stress certain facts about pneumonia caused by hemolytic streptococci, some of the outstanding features will be reviewed here.

Pneumonia due to hemolytic streptococci may either be a primary infection or be secondary to some other infection of the respiratory tract, such as acute coryza, epidemic influenza, measles, pneumococcic pneumonia or chronic disease of the respiratory tract. It commonly produces diffuse interstitial bronchopneumonia and is complicated by empyema in at least 25 per cent of cases. The fatality rate without chemotherapy varies between 25 and 40 per cent. With chemotherapy the fatality rate both for pneumonia and for empyema can be reduced; the course of the disease, however, may be indeterminate.

Inasmuch as this type of pneumonia is so often secondary to other infections, every effort should be made to protect patients with the infections just mentioned from coming in contact with those persons who carry hemolytic streptococci or who have clinical streptococcic disease.

*Bacteremia.*—In all, 37 different strains of hemolytic streptococci were isolated from the circulating blood, and we were able to type 32 of them. The results are recorded in table 2. As might be anticipated, the

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16. Keefer, C. S.; Rantz, L. A., and Rammelkamp, C. H.: Hemolytic, Streptococcal Pneumonia and Empyema: A Study of Fifty-Five Cases with Special Reference to Treatment, *Ann. Int. Med.* **14**:1533, 1941.

general distribution of the specific types in this study was the same as in the group as a whole. The common types, in order of frequency, were 15, 11, 13, 25 and 27.

The fatality rate for the group as a whole was 57 per cent. In another paper, one of us (C. S. K.) with associates<sup>17</sup> pointed out that without chemotherapy the fatality rate in bacteremia caused by hemolytic streptococci was 72 per cent and the factors influencing fatality were age, portal of entry, the presence of debilitating disease and the accessibility of the focus of infection for surgical drainage. Since all of the patients with bacteremia were treated with sulfanilamide, it was of interest to analyze the other factors which are known to influence prognosis under these circumstances.

TABLE 5.—*Correlation Between Fatality Rate and Age in Patients with Bacteremia*

Age, Yr.	Outcome		Total
	Recovery	Death	
10-20.....	7	0	7
21-30.....	2	2	4
31-40.....	5	3	8
41-50.....	1	5	6
51-60.....	1	3	4
61-70.....	..	7	7
70 or over.....	..	1	1
Total.....	16	21	37

Fatality rate for patients under 40 years, 26 per cent  
 Fatality rate for patients over 40 years, 88 per cent

Of the 16 patients who recovered, 14 were under 40 years of age and none was over 60 years of age. Of the 21 patients who died, 16 were over 40 years of age; the ages of the remaining 5 varied from 21 to 40 years. In the patients under 40 who died such conditions as acute endocarditis, alcoholism, puerperal sepsis or cirrhosis of the liver were present.

The fatality rate for patients under 40 years was only 26 per cent, whereas for those over 40 years it was 88 per cent, a striking difference. This is particularly impressive when it is compared with fatality rates for patients treated without sulfanilamide, since here the fatality rate for those under 40 years is about 60 per cent (table 5).

There did not seem to be any correlation between the type of organism and the frequency with which the blood was invaded when one took

17. Keefer, C. S.; Ingelfinger, F. J., and Spink, W. W.: The Significance of Hemolytic Streptococcal Bacteremia: A Study of Two Hundred and Forty-Six Patients, *Arch. Int. Med.* **60**:1084 (Dec.) 1937.



into account such factors as age, focus of infection and the presence of debilitating disease (table 6). For example take type 11. Of 6 patients with bacteremia caused by organisms of type 11, all died. With the exception of 1 patient who had puerperal sepsis, all of the patients were over 40 years of age and in all of them the portal of entry was the skin. We have shown previously that bacteremia following infections of the skin and the subcutaneous tissues is always associated with a high death rate in patients over 40 years of age. The importance of age is also brought out in the study of other types (type 15). Of the 5 patients who recovered, 4 were under 20 years of age and the other was 29 years old. Of the 10 patients who died, all but 1 were over 40 years of age, and the site of the infection was such that it could not be localized and drained surgically.

TABLE 6.—*Correlation Between Fatality Rate, Type of Invading Hemolytic Streptococcus and Age in Patients with Bacteremia*

Type	Age			
	Under 40 years		Over 40 Years	
	Recovered	Died	Recovered	Died
15.....	5	1*	0	9
11.....	0	1†	0	5
12.....	0	2	0	3
27.....	0	0	0	1
25.....	0	2‡	..	..
1.....	2	1§	0	0
13.....	1	0	0	1
Unidentified types .....	4	0	1	0

\* Died of heart disease.

† Died of puerperal sepsis.

‡ Died of bacterial endocarditis and of chronic alcoholism.

§ Died of chronic alcoholism.

No evidence was obtained, therefore, which indicated that any particular type was more likely to invade the blood. Invasion of the blood was correlated more often with age, the focus of infection and the general condition of the patient than with the type of invading organism.

*Abscesses.*—Hemolytic streptococci were obtained from 58 abscesses, and 74 per cent of the strains were typed. They included, in order of frequency, types 11, 1, 13, 15, 27 and 28. These abscesses occurred in all parts of the body, including the throat, neck, extremities, pelvis, other bones, scrotum and the perirenal region.

*Rhinitis.*—Forty-one patients had rhinitis after scarlet fever. The common types causing this complication were type 13, isolated sixteen times; type 15, isolated six times, and an unidentified type, isolated 9 times. Other types were 2, 11, 25 and 10. Rhinitis was encountered in 16 per cent of all patients with infection caused by hemolytic streptococci of type 13.

*Puerperal Sepsis.*—Only 1 patient in this series had puerperal sepsis, but the important studies of Colebrook<sup>11a</sup> and of Butler and Hill<sup>6a</sup> are well worth reviewing in connection with this study, since they add valuable information concerning the mode of infection and the spread of puerperal sepsis. Colebrook's monograph is filled with information of the greatest value and importance, and every physician and obstetrician should be familiar with the facts that she brings out, in order that the occurrence of puerperal sepsis may be reduced or prevented. Some of the outstanding facts are the following ones:

1. Organisms which cause puerperal sepsis are not found in the vagina at the beginning of labor.

2. The most important sources of infecting organisms are in the human respiratory passages and in septic foci of infection.

3. The extragenital source of infection may be in the respiratory passages (nose or throat) of (a) the patient herself, (b) the members of her family or (c) her professional attendants. These persons may be healthy carriers, or they may have head colds with hemolytic streptococci in the nose and/or throat.

4. Organisms may be conveyed from the nose and throat of the patient or of "familial" contacts by means of her own hands or perhaps by towels which are contaminated by the secretions of the nose or throat.

5. Every parturient woman runs the risk of infection when her confinement is conducted in an infected environment. Attendant contacts are most frequent; household contacts are next in frequency, and auto-infection from extragenital sources are third.

6. Puerperal sepsis is most common during the season of the year when other infections caused by hemolytic streptococci are prevalent, and the types are those most frequently encountered in these infections.

Colebrook found types 1, 2, 5, 14 and 25 to be the commonest types isolated, but among 85 strains tested, 18 different types were identified. In Australia Butler and Hill<sup>6a</sup> were able to type 38 of 68 strains which were isolated from patients with puerperal sepsis. Types 22 and 27 and 1 type called "Woodbury" were responsible for the infections.

Diddle, Trussell and Plass<sup>9a</sup> described an epidemic of scarlet fever and other infections caused by hemolytic streptococci in an obstetric ward. An examination of this paper confirms the fact that puerperal sepsis is due to the spread of infection from the nose and throat to the uterus, as well as to or from other areas of the body. The predominating organism in this epidemic was type 3, and the original case was that of a parturient woman with a severe infection of the upper respiratory tract, which had been acquired during an unreported contact with a relative in the prodromal stage of scarlet fever. It was of interest that of the

persons who were exposed in the ward, an infection of the upper respiratory tract developed in 14 infants and severe tracheobronchitis due to hemolytic streptococci developed in 7 of the 14. Of the 66 adults who harbored hemolytic streptococci, 14 had typical scarlet fever, 2 had puerperal endometritis, 13 had pharyngitis, 5 had rhinitis and 32 were asymptomatic carriers. This epidemic illustrates how the organisms may spread from 1 person to a group and produce a wide variety of clinical infections.

De Waal<sup>51</sup> reported that the commonest types causing puerperal sepsis in Scotland are types 1, 4 and 28. Only 22 of 50 strains could be typed, but the type of hemolytic streptococci which predominated usually varied with the season of the year and reflected the epidemic type which was present in patients with scarlet fever at the time.

#### RELATION OF SPECIFIC TYPES TO SEVERITY OF INFECTION AND COMPLICATIONS

Attempts have been made by several investigators to correlate the severity of infection and the incidence of complications with certain specific types of streptococci. Gunn and Griffith<sup>5d</sup> in 1928 stated that type 1 seemed to produce the most severe disease and the most complications and type 2 was likely to cause nephritis and endocarditis. The number of cases studied was small. De Waal,<sup>51</sup> on the other hand, found that type 4 produced the most severe infections in Scotland and type 1 was responsible for mild attacks of scarlet fever. He stated that the complication rate in infections caused by organisms of type 1 was higher than that in infections caused by type 4 organisms and the complications in infections caused by type 1 organisms were frequently due to cross infection with those of type 4. He expressed the opinion that these organisms may become increasingly virulent or avirulent, depending on factors which are at present unknown.

It is a difficult matter to assess the relative severity of different infections unless one considers bacteremia and death as indicative of the most serious infections, as well as the total duration of the infection and the complications in those patients who survive. Even when one takes bacteremia as a criterion for severity of infection, it becomes apparent that there are many factors other than the type of infecting organism which influence the outcome. While blood cultures were not made for all patients who were studied in this group, bacteremia was present in 4.5 per cent of those for whom cultures were made.

The frequency with which various types were isolated from the blood varied from 1.4 per cent in type 13 to 8.0 per cent in types 25 and 27. That is to say, 1.4 per cent of all the type 13 strains we studied

were isolated from the circulating blood. On more careful analysis it was found that factors other than specific type determined the frequency of bacteremia. These were the age of the patient, the portal of entry and the general condition of the patient.

Other methods of correlating the severity of infection with the characteristics of the organisms have been used by Butler and Hill <sup>6a</sup> and White, Rudd and Ward.<sup>6b</sup> These investigators have found that encapsulated strains of hemolytic streptococci have greater infectivity than noncapsulated ones, and Butler and Hill expressed the opinion that encapsulated strains caused more severe infections and showed that 21 of 22 strains isolated from the blood stream were capsulated. White, Rudd and Ward were in agreement that capsulated strains are more likely to cause infection, perhaps due to their ability to resist phagocytosis, but asserted that once the tissues are invaded the noncapsulated organisms are just as virulent as capsulated strains.

In the present state of knowledge, it would be premature to say that some types of hemolytic streptococci are invariably more invasive and virulent than others. It does seem clear, however, that certain strains of hemolytic streptococci, regardless of their type, are more invasive and more virulent than others and that this is due in part to the organism's ability to resist phagocytosis. Before this question can be settled, it will be necessary to study and analyze many cases in which both the characteristics of the organism and the factors in the host are taken into consideration.

The determination of the relation between specific types and complications is a difficult problem, since many of the late suppurative complications are caused by a new type of organism or by cross infection. This aspect of the subject has been investigated by Gunn and Griffith,<sup>5d</sup> Brown and Allison,<sup>5j</sup> de Waal,<sup>5i</sup> Bailey<sup>9c</sup> and others. Brown and Allison<sup>5j</sup> made a most thorough study of the question both of complications and of relapses in scarlet fever and pointed out that no reinfections occurred in single-bed rooms or in wards in which the patients were all infected with the same type of organisms. In one ward of 47 patients, complications occurred in 20. In 18 the complication was due to a different type of organism from that which caused the original infection. In another group of 15 patients the infection was latent; that is, a different type of streptococcus was found without signs of complications. In 10 patients who showed relapses a new type of organism was found in the throat. It has been demonstrated by Gunn and Griffith<sup>5d</sup> that relapses of scarlet fever may occur in patients with a different type of organism who failed to give a negative reaction to the Dick test after the initial attack. Of considerable importance in the com-

plications due to a different type of streptococcus was the time of their occurrence. Sixteen of the 18 complications occurred during the second, the third and the fourth week of illness.

De Waal<sup>51</sup> has reported new types in 61 per cent of complications of scarlet fever in Edinburgh and in this way indicates that complications are frequently caused by reinfections. His results confirm those of Brown and Allison.<sup>53</sup>

Bailey<sup>50</sup> stated that he was unwilling to accept the fact that complications are due to cross infection or reinfection, and based his opinion on his own studies, which were made in 1934 and 1935. He found that as many as 57.6 per cent of patients who were admitted to a hospital and in whom complications did not develop left the hospital with a type of streptococcus different from that which they harbored on admission. In another group of 18 patients with complications, 9 had a different type of streptococcus in the throat. He reported a general complication rate of 36 per cent  $\pm$  2.3 in 197 patients. Among 72 patients showing a type of hemolytic streptococcus on discharge which was different from that causing the disease, the complication rate was 25 per cent  $\pm$  3.4. He apparently felt so confident of the isolation technic in his hospital that he explained the differences in the types which were isolated early and late in the course of the disease on a basis of transmutation rather than cross infection. Certainly from the data presented by Bailey one may conclude that a patient may have a different type of streptococcus in the throat late in the course of the disease, with or without complications. This is in concurrence with the observations of others. There is no agreement, however, that organisms change from one type to another during the course of the disease. There seems to be little doubt, then, that complications may be due to the same type as that causing the original infection or that they may be due to a different type. Also, after an uncomplicated infection a patient may continue to carry the same type of organism in the throat when he is discharged from the hospital or he may carry one of a different type.

Our own observations concerning the relation of reinfection and complications were of interest. In 34 patients the type of the causative organism was known at the beginning of the infection and also at the time of the complication. The results are shown in table 7. In 12 patients the same type of hemolytic streptococcus was isolated from the throat during the original infection and during the complication in the first two weeks of the illness, and in only 3 was a different type found in the throat and middle ear. After the second week, however, there were only 2 complications due to the same type, whereas 16 were due to a different type. These observations certainly suggest that many of the late complications of scarlet fever are due to a different type of

organism from that isolated originally. When the complication occurs during the first two weeks, it is generally due to the same type of organism causing the initial infection. In all, 55 per cent of the complications were caused by a different type of streptococcus.

*Recurrent Scarlet Fever.*—Two patients had recurrent scarlet fever. Neither patient had received either sulfanilamide or convalescent serum, and in both cases the type of hemolytic streptococcus isolated during the recurrence was different from that which was isolated during the primary attack. In 1, types 8 and 15 were responsible for the 2 attacks, and in the other types 12 and 13.

There were 20 patients in whom no complications were present and in whom we typed the organism at the time of the initial infection and at the time of discharge. The same type was present on discharge in

TABLE 7.—*Relation Between Types of Hemolytic Streptococci Found During Original Infection (Scarlet Fever) and During Complication*

Interval Between Original Infection and Complication, Days	Same Type Isolated	Different Type Isolated
Same day	7	0
1-7	4	1
8-15	1	2
16-21	1	5
22-28	1	7
28	..	4
Under 2 weeks	Same type	12
	Different type	3
Over 2 weeks	Same type	2
	Different type	16

12 patients, but a different type was found in 8. This suggests that a patient with scarlet fever may become a carrier of an organism of a different type from that causing the original infection. While we were unable to trace the source of the cross infections in these patients, the types which were isolated during the complication were prevalent in the hospital at the same time, so that the most likely explanation, taking everything into consideration, is that the cross infection took place either directly from other patients by means of transmission through the air or by contact with attendants. That this is the usual explanation there can no longer be any doubt.

Indirect evidence for cross infection is found in a study of the types in multiple cases in the same family. There were ten families in which more than 1 member had scarlet fever at the same time. In each family group the same type of hemolytic streptococcus was responsible for the scarlet fever. This fact has been stressed by Bradley<sup>50</sup> and de Waal.<sup>51</sup>

From our own studies and those reported in the literature, the relation of specific types to the severity of infections caused by hemolytic streptococci and complications may be summed up as follows:

1. There is insufficient evidence at present to state whether any specific type is likely to cause more serious disease or more frequent complications. It would appear that other factors aside from the specific type of organism are equally important, such as the presence or absence of capsules, age of the patient, portal of entry and whether the blood is invaded by the organism.

2. The chief value of typing at present seems to be in studying the epidemiologic aspects of infection. This includes its mode of spread and the cause and mechanism of complications. All of these facts aid in prophylaxis.

3. When multiple infections caused by hemolytic streptococci occur in families, they are usually due to organisms of the same type.

4. When complications occur early in the course of the infection, i.e., during the first two weeks, the same type of streptococcus is usually found in the area of complicating infections. When the infection occurs after the second week, a different type of organism is frequently found. These observations suggest that many late complications are due to cross infections and, therefore, are true reinfections.

5. A patient can become a carrier of a different type of streptococcus from that causing his illness without displaying any signs of complications.

#### STREPTOCOCCIC DISEASE CAUSED BY ORGANISMS OF DIFFERENT TYPES

*Type 1.*—Streptococci of this type were isolated chiefly from patients with scarlet fever, tonsillitis, otitis media and mastoiditis. They were found also in persons with erysipelas and pneumonia and in circulating blood. They caused otitis media in 20 per cent of the patients with scarlet fever. They were more often the cause of otitis media without preceding scarlet fever than with preceding scarlet fever. On three occasions type 1 organisms were isolated from the circulating blood. There was no evidence in the small number of patients studied that infection caused by this type was more severe than infections caused by other types.

*Type 2.*—Organisms of this type were isolated mainly from persons with scarlet fever, otitis media, mastoiditis and pneumonia. The infections were relatively mild without complications.

*Type 11.*—Organisms of this type were third in order of frequency in the entire series. They caused scarlet fever, tonsillitis, otitis media, abscesses and erysipelas and invaded the blood of 6 patients. The

incidence of otitis media was greater without preceding scarlet fever than it was with it. This was the commonest specific type isolated from persons with mastoiditis and from localized abscesses. The invasion of the blood occurred in elderly persons with cellulitis or cutaneous lesions.

*Type 13.*—This type was second in order of frequency, causing mainly scarlet fever, tonsillitis, otitis media and mastoiditis. Twelve per cent of the infections due to this type were scarlet fever complicated by otitis media. Organisms of type 13 were also isolated from persons with pneumonia and empyema and from abscesses and the circulating blood.

*Type 15.*—This was the commonest type, and the organisms were isolated from persons with scarlet fever, otitis media and mastoiditis and pneumonia and empyema and from circulating blood and abscesses. It was the cause of erysipelas and meningitis in 1 patient each. This is one of the common types causing scarlet fever in Scotland and in Australia.

*Type 25.*—Organisms of this type were isolated from persons with otitis media and mastoiditis, tonsillitis and scarlet fever and from abscesses and the circulating blood.

*Type 27.*—Streptococci of this type had the same distribution as those of type 25.

*Other Identified Types.*—Types 5, 6, 8, 9, 10, 14, 19, 21, 26, 28 and 29 were responsible for a few of the infections listed in the table.

*Unidentified Types.*—Types which could not be identified accounted for 180 infections.

#### COMMENT

We may now ask the question, what have these observations contributed to the information concerning infections caused by hemolytic streptococci and of what value is the typing of hemolytic streptococci in the study of various diseases? It will be generally agreed that the treatment of such infections has been revolutionized during the past six years because of the introduction of sulfanilamide and its derivatives. It is plain, however, that the fatality rate continues to be high in certain of these infections, especially when they occur in aged persons, and the time lost from these different diseases continues to be considerable. The problem of prevention of infection caused by hemolytic streptococci, therefore, becomes one of the major considerations in this field. In order to prevent a disease, its cause and mode of spread must be known. By means of specific typing, information concerning the mode of spread and the sources of infection can be obtained. At present, this would appear to be its greatest field of application. It may also be of value in explaining the difference in severity of various infections, although



from the evidence that has accumulated thus far it appears that there are other factors aside from specific types which are equally or more important.

Typing of hemolytic streptococci has also settled the long controversy concerning the specificity of hemolytic streptococci with reference to particular diseases. It is now clear that factors other than the organism are operative in the production of various clinical entities. The same specific type of hemolytic streptococcus may cause scarlet fever, tonsillitis, otitis media, mastoiditis, erysipelas or puerperal fever. The view that specific streptococci are responsible for specific diseases is no longer tenable.

Typing of organisms has also assisted in explaining relapses in patients with scarlet fever and late complications, since relapses are due to a reinfection by a different type of organism in a person in whom toxic immunity has failed to develop, and many of the late complications are due to reinfections.

Finally, it has provided suggestions which should be of great assistance in controlling the spread of infections.

We may now discuss some of the facts which are concerned with the mode of spread of diseases caused by hemolytic streptococci and which have been placed on a firm foundation by means of specific typing and accurate identification of organisms. The normal habitat of the hemolytic streptococcus is in the throat and nose, so that there are many carriers in the general population. The carrier rate increases during the winter months when streptococcic diseases are prevalent and when healthy persons come in contact with patients with these diseases. Such infections are more common when head colds are frequent. A person may be predisposed to infection by hemolytic streptococci; if he carries the organisms prior to the development of a cold, he can disseminate them more readily when the cold is active. The carrier state may be permanent or transitory, and the specific types carried may vary from time to time, depending to some extent on the carrier's contacts.

Since the normal habitat of hemolytic streptococci is in the throat and nose, and since the commonest sites for acute infections due to these organisms are in the same region of the body, it is not surprising that infections caused by hemolytic streptococci, regardless of their location, have their original source in the nose or throat. Therefore, carriers, and especially persons with head colds, who harbor hemolytic streptococci or persons with tonsillitis, pharyngitis, sinusitis or scarlet fever may all serve as sources of infection. From the nose and throat, infection may spread from one person to another by means of contact, i.e., transmission of air-borne organisms (coughing, sneezing, dust particles), contamination of the hands or fomites (towels, toys, food) with infected material.

By means of specific typing, then, it has been possible to show that hemolytic streptococci are spread in these ways. A few examples will serve to support these statements:

1. Multiple infections caused by hemolytic streptococci in families and schools or other institutions are usually due to the same type of organism, regardless of the clinical forms of the disease.

2. Epidemics of infection caused by hemolytic streptococci can often be traced to a single patient with the disease.<sup>18</sup> A single patient with sore throat or scarlet fever may be responsible for other instances of similar disease or for puerperal sepsis, tracheobronchitis, pneumonia or erysipelas in contacts.

3. Puerperal sepsis may arise from persons who carry hemolytic streptococci in their throats or have septic foci. They may also arise from the patient herself; that is, the uterus may be infected through the medium of the patient's hands if she carries organisms in her throat.<sup>11a</sup>

Examples of this kind might be multiplied many times, but these serve to illustrate how infections may spread.

What can one do, then, to prevent the spread of hemolytic streptococci and reduce the number of cases of disease?

The clinical picture of scarlet fever can be prevented by prophylactic inoculation with toxin or toxoid. Whether such prophylactic inoculation reduces the incidence of infections in the throat without a rash or the other clinical manifestations of intoxication is difficult to decide with the evidence at hand, since in most of the reports which have dealt with the subject of prophylactic inoculation, the authors stressed the decrease in the frequency of the clinical picture of scarlet fever and made no statement about the incidence of streptococcic pharyngitis or tonsillitis in an inoculated group. According to some reports, the incidence of tonsillitis has remained the same in an inoculated group as in a non-inoculated group. According to others, it has been reduced. From the study of epidemics of scarlet fever in institutions, there seems to be good evidence that the clinical picture of scarlet fever does not develop in the children who give negative reactions to the Dick test, but that tonsillitis is prevalent and is caused by the same type of organism as that causing scarlet fever in others. In any event, it would seem to be a wise practice to immunize all professional attendants who give positive reactions to the Dick test and who come in contact with persons with scarlet fever and thus to prevent the symptoms and signs due to the toxin should an infection of the throat develop in such attendants.

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18. Footnote 9 *d*, *e* and *g*.

Attempts have been made to protect groups who are susceptible to tonsillitis by vaccination<sup>19</sup> or by the use of sulfanilamide.<sup>20</sup> So far the evidence that either one of these measures is effective is too meager to warrant any conclusions. One must remember that the most susceptible persons are children between the ages of 5 and 15 years and those who are commonly exposed (nurses, attendants, physicians, school children and children in institutions).

The prevention of the spread of infections by contact can be minimized by means of isolation. The isolation of patients with scarlet fever and tonsillitis is easier than the isolation of patients with streptococcic pharyngitis and persons with head colds who carry organisms, because the patients in the former group have constitutional symptoms and a clinical disease which is readily recognized as being due to hemolytic streptococci. Even with good isolation technic in wards in a hospital, cross infection is not infrequent. Whether the methods of air conditioning or air sterilization in institutions and schools will reduce these cross infections still further only additional study will decide. In any event, before these infections can be reduced it will be necessary to develop practical methods for the prevention of the spread of organisms from one person to another.

#### SUMMARY AND CONCLUSIONS

During the years 1938 and 1939, 819 strains of group A hemolytic streptococci were studied in relation to their type specificity, the disease, the severity of infection and the occurrence of complications. The organisms were isolated from persons with scarlet fever, tonsillitis, erysipelas, abscesses, pneumonia, meningitis, and otitis media, with or without associated mastoiditis, and from nasal swabs and circulating blood. Of the 819 strains, we were able to type and identify 79 per cent with the serums that were available. As a result of these studies the following facts emerged:

1. The commonest types causing disease were 15, 13, 11, 1, 2, 25 and 27.
2. A number of types which cause disease are not included in the original Griffith strains.
3. The distribution of specific types varied from that which has been reported elsewhere. This is what might be expected in view of the

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19. Bloomfield, A. L., and Felty, A. R.: Prophylactic Vaccination Against Acute Tonsillitis, *Bull. Johns Hopkins Hosp.* **12**:1473, 1939.

20. Thomas, C. B.; France, R., and Reichsman, F.: Prophylactic Use of Sulfanilamide in Patients Susceptible to Rheumatic Fever, *J. A. M. A.* **116**:551 (Feb. 15) 1941.

previous studies from other countries, since it has been shown that the predominating types vary from one community to another, from year to year and from epidemic to epidemic.

4. The same type may be responsible for different clinical diseases, that is, scarlet fever in 1 person, tonsillitis in another, erysipelas in a third and rhinitis in a fourth. This is striking in family epidemics of infection caused by hemolytic streptococci.

5. When one or more types are predominant in any community, the same types are usually isolated from persons with various diseases, such as scarlet fever, tonsillitis and otitis media.

The various types which were isolated during this study were discussed from the angle of the disease they caused, the severity of the infection and the ensuing complications. The following facts are significant:

1. When multiple instances of infection occur in families, institutions and schools, they are usually due to the same type of organism.

2. Epidemics of puerperal sepsis, tonsillitis, scarlet fever or other streptococcic infections can be traced to their source by means of typing the organism in different persons, usually contacts.

3. There is insufficient evidence available at present to determine whether some types cause more serious infections or a greater number of complications than others. There is substantial evidence, however, to suggest that factors other than the specific type of causative organism are important in determining the severity of infection and the incidence of complications. They include the age of the patient, the portal of entry, the presence or absence of debilitating disease, the general condition of the patient and the occurrence of reinfection.

4. When complications occur during the course of scarlet fever, they may be due to the same type of organism which caused the initial infection or to a different type. Complications occurring during the first two weeks of illness are frequently due to the same type; those developing later are often due to a different type. These observations suggest that late complications are due to reinfection.

The significance of these observations is discussed:

Miss Marjorie Jewell and Miss Eleanor Fleming gave technical assistance. Dr. W. G. Malcom, of the Lederle Laboratories, Inc., supplied us with the specific typing serums which were used in this study.

# EFFECT OF MORPHINE AND DILAUDID ON THE ILEUM AND OF MORPHINE, DILAUDID AND ATROPINE ON THE COLON OF MAN

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Plant and Miller <sup>1</sup> originally demonstrated that morphine in ordinary doses does not place the human intestine and colon at rest. This observation has been adequately confirmed. However, some authors have reported that the stimulation of motility, depending on the dose, is brief (twenty to sixty minutes) and is followed by depression,<sup>2</sup> and others have observed that the stimulation is of much longer duration.<sup>3</sup> It has been amply demonstrated that morphine delays the passage of material through the alimentary tract,<sup>4</sup> but the cause of the delay has not been clearly established.

Functionally, gastrointestinal motility is of two general types, namely, propulsive and nonpropulsive.<sup>5</sup> In the dog morphine affects these two

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From the Department of Physiology and Pharmacology, Northwestern University Medical School.

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Dr. Peter Rosi aided us in securing subjects.

1. Plant, O. H., and Miller, G. H.: Effects of Morphine and Some Other Opium Alkaloids on the Muscular Activity of the Alimentary Canal, *J. Pharmacol. & Exper. Therap.* **27**:361, 1926.

2. (a) Abbott, W. O., and Pendergrass, E. P.: Intubation Studies on the Human Small Intestine, *Am. J. Roentgenol.* **35**:289, 1936. (b) Hertzler, A. E.: The Effect of Morphine on Intestinal Motility, *J. Kansas M. Soc.* **40**:197, 1939.

3. (a) Orr, T. G., and Carlson, H. E.: Effect of Morphine on the Movements of the Small Intestine and Sphincter Muscles, *Arch. Surg.* **27**:296 (Aug.) 1933. (b) Yonkman, F. F.; Hiebert, J. M., and Singh, H.: Morphine and Intestinal Activity, *New England J. Med.* **214**:507, 1936.

4. (a) Meyers, G. N., and Davidson, S. W.: An Investigation of the Effects of Certain Substitutes for Morphine and Heroin upon the Passage of Food Along the Alimentary Tract of the Human Subject, *J. Hyg.* **38**:432, 1938. (b) Pancoast, H. K., and Hopkins, A. H.: Effect of Moderate Doses of Some Opium Derivatives on the Gastro-Intestinal Tract of Man, *J. A. M. A.* **65**:2220 (Dec. 25) 1915.

*(Footnotes continued on next page)*

types of motility differently.<sup>6</sup> The propulsive activity is temporarily increased and is then abolished, while nonpropulsive activity is increased for several hours. Whether morphine similarly affects the motility of the human small intestine and colon has not been adequately determined, nor has the action of dilaudid been similarly studied. We have investigated these problems and, in addition, have ascertained the effect of atropine on the changes in motility induced in the colon of man by morphine. A similar study has been made adequately by us on the dog with the idea in mind that the morphine-induced, hypertonic, nonpropulsive type of motility might be used to assay the effectiveness of antispasmodics on the colon of man.<sup>6b</sup>

#### PROCEDURE AND METHOD

*Small Intestine.*—We employed as a subject a patient who had undergone an ileostomy two years previously for ulcerative colitis. The patient was in excellent physical condition, was 38 years of age and weighed 140 pounds (63.5 Kg.). He was kept under our observation and dietary control for an experimental period of three months. During these three months experiments of three hours' duration were conducted twice daily.

A balloon or balloons in tandem were inserted through the orifice of an ileostomy bag. This permitted observation of the nonpropulsive motility, quantitative collection of the ileal discharge and quantitative evaluation of propulsive motility.

*Colon.*—Four men on whom colostomy had been performed six to eighteen months previously were the subjects. The rectum and one half of the sigmoid colon had been removed for carcinoma. The patients were in excellent physical condition, and no evidence of metastases was manifest. For six months 1 or 2 experiments, each three hours in duration, were conducted daily.

One or two balloons in tandem were inserted through the fistula into the descending colon; thus, the motility of the colon caudad the splenic flexure and 3 or 4 inches (7.5 to 10 cm.) cephalad the fistula was studied. More balloons in tandem or the motility of the transverse colon was not studied because on several occasions the balloon cephalad was tied by the colon into a simple knot, which rendered it difficult to remove in the presence of the hypertonicity of the colon induced by drugs. The balloons were all inflated according to a standard technic.<sup>6b</sup> Propulsive motility was evidenced and recorded by the outward movement of the tube from the fistula and the passage of gas and feces.<sup>7</sup>

*Controls.*—The patients were highly cooperative and permitted the repetition of tests many times. For example, 22 three hour balloon studies serving as a

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5. (a) Quigley, J. P.; Highstone, W. H., and Ivy, A. C.: A Study of the Propulsive Activity of a Thiery-Vella Loop of Intestine, *Am. J. Physiol.* **108**: 151, 1934. (b) Reid, P. E.; Ivy, A. C., and Quigley, J. P.: Spiral Propulsion of a Bolus in the Intestine, *ibid.* **109**:483, 1934.

6. (a) Templeton, R. D., and Adler, H. F.: The Influence of Morphine on Transportation in the Colon of the Dog, *Am. J. Physiol.* **131**:428, 1940. (b) Adler, H. F., and Ivy, A. C.: Morphine-Atropine Antagonism on Colon Motility in the Dog, *J. Pharmacol. & Exper. Therap.* **70**:454, 1940.

7. Adler, H. F.; Atkinson, A. J., and Ivy, A. C.: A Study of the Motility of the Human Colon: An Explanation of Dysynergia of the Colon, or of the "Unstable Colon," *Am. J. Digest. Dis.* **8**:197, 1941.

control series were made on the patient who had undergone ileostomy. Sixty-seven similar control studies were made on those on whom colostomy had been performed. Hence, we were able to obtain as complete a picture of the motility of the human colon, with individual spontaneous variations, as of the canine colon.

*Types of Motility Observed in the Human and the Canine Colon.*—The three types of motility (fig. 1) manifested by balloon records of the human and the canine colon are similar.<sup>8</sup> Type I contractions are rather rapid and may occur in the presence of high or low tone and in any segment of the colon. Type I contractions on high tone are frequently seen after the administration of morphine. This type is rarely associated with the propulsion of contents, unless it occurs rather suddenly and in an exaggerated form, as after the administration of morphine. Even then, after the initial change of tonus level, propulsion does not occur if the tonus level is maintained. The type II contractions are characterized by their larger amplitude, longer duration and the superimposition of type I contractions. This type of contraction is frequently propulsive in nature. Whether contents are propelled, however, depends on the amplitude of the contraction, on the consistency of the contents and on the relation the contracting

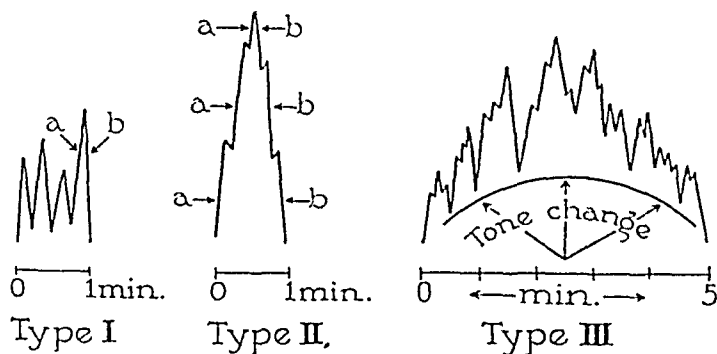


Fig. 1.—A diagrammatic representation of the manner in which complex contraction patterns are built up from more simple contractions. Type I contractions occur at the rate of 3 to 8 per minute and consist of a rapid contraction (a) followed by rapid relaxation (b). Type II contractions consist of contraction limbs made up of superimposed type I contractions. Type III contractions have a pattern consisting of type I and II contractions superimposed on a definite change in tonus.

segment bears to the motility of the adjacent segments. For example, if a segment manifests a type II contraction and the adjacent segment caudad exhibits type I activity on tone, the former contraction does not cause propulsion of contents unless motility of the segment caudad suddenly changes toward type II. Type III contractions are characterized by a definite tonus change of variable duration on which type II contractions of varying amplitude are superimposed. The change in tonus, or slow contraction, on which the type II contractions are superimposed usually does not last longer than twelve minutes in man. When this type of contraction occurs, it is usually followed by a period of quiescence.<sup>8</sup>

8. Templeton, R. D., and Lawson, H.: Studies on the Motor Activity of the Large Intestine, *Am. J. Physiol.* **96**:667, 1931. Adler, Atkinson and Ivy.<sup>7</sup>

The initial type II contractions which are manifested during the rise in tone are chiefly responsible for the propulsion that occurs during this type of contraction.<sup>9</sup>

It is important to point out that the type of motility of one segment may be quite different from that of adjacent segments. Significant propulsion, as occurs in "mass peristalsis," is not exhibited until the motility of adjacent segments becomes coordinated, so that type II waves pass successively in a synergized manner to and over the more caudal segments. The importance of this concept in relation to the explanation of the "irritable colon," which is viewed as "dyssynergia of the colon" has been indicated in a previous article.<sup>7</sup>

## RESULTS

### ILEUM

*Effect on the Motility of the Human Ileum of the Intramuscular Injection of Five, Eight, Ten and Sixteen Milligram Doses of Morphine Sulfate.*—The subject ate the same breakfast and lunch each day. Soon after he had finished breakfast the residue of the previous evening dinner was passed into the ileostomy bag. The breakfast taken at 8 a. m. would normally begin to appear definitely after 11 a. m., the subject being under observation from 9 a. m. to about 12 noon. At 12 noon lunch was ingested, and soon after the residue from breakfast was passed. The subject was then under observation until 4:30 p. m. At about 4 or 4:30 p. m. the luncheon residue would begin to appear in the ileostomy bag.

**Balloon Records of Motility:** After a control record was obtained for twenty to forty minutes, the morphine sulfate was injected. During the control period the ileum was relatively quiet because of the aforementioned previous evacuation. After a latent period of five to twenty minutes, depending usually on the size of the dose of morphine, the tone of the ileal segment started to increase. The tonus level rose to a plateau, at which variations in tone occurred on which rhythmic contractions of larger amplitude than those of the control period were manifested at a rate of 3 to 9 per minute (fig. 2 A). This type of response was observed in 12 of 18 experiments with the various doses of morphine. In 3 experiments no significant change occurred, and in 3 there was a decrease in tone.

**Propulsive Motility:** In the dog shortly after the injection of morphine an increase in tone and propulsive motility occurs which lasts twenty or thirty minutes, after which propulsive activity decreases or is absent and nonpropulsive activity and tone continue to be augmented for several hours. The early increase in propulsion is less evident in the ileum than in the jejunum.<sup>5a</sup>

9. Adler, H. F., and Templeton, R. D.: The Correlation of Activity and Transportation in the Colon of the Dog, *Am. J. Physiol.*, **128**:514, 1940. Adler, Atkinson and Ivy.<sup>7</sup>



According to our observations on the human subject, no increase in propulsive activity occurred after the injection of morphine. The propulsive activity was diminished throughout the period of observation.

Amount of Contents Collected from the Ileostomy Bag: In correlation with what one would predict from the motility records of the lower portion of the ileum, it was found that less material was ejected into the ileostomy bag after the administration of morphine than when morphine

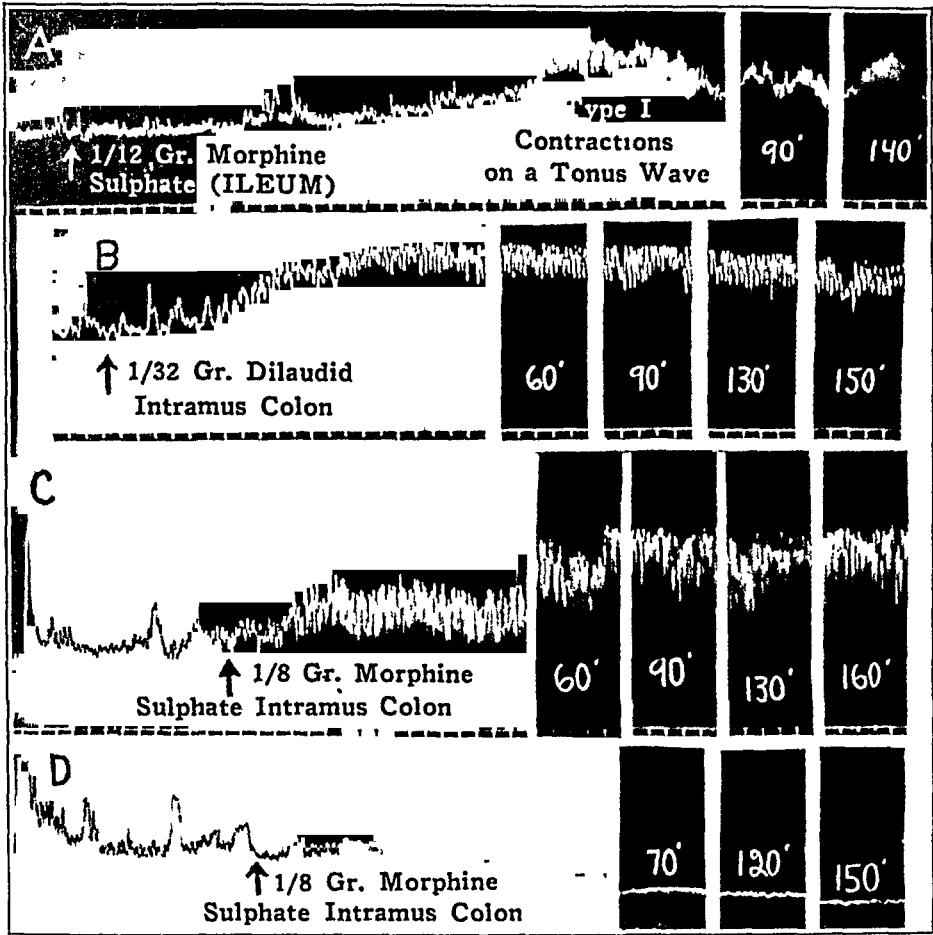


Fig. 2—*A*, the reaction of the human ileum to  $\frac{1}{12}$  grain (0.005 Gm.) of morphine sulfate includes a rise in tonus and the appearance of type I contractions. *B*, the reaction of the human colon to 2 mg. of dilaudid hydrochloride. A rise in tonus and type I contractions (at a slower rate than in *A* or *C*) are evident. *C*, the reaction of the human colon to 8 mg. of morphine sulfate includes the appearance of type I contractions and a rise in tone. *D*, the reaction of the colon of the patient referred to in *C* to another 8 mg. dose of morphine sulfate. There is a definite decrease in tonus, but small type I waves are present.

was not given. During the 22 three hour control experiments an average of 90 cc. of contents was collected, the range being 72 to 115 cc. In the 18 three hours experiments with morphine an average of 35.6 cc. of con-

tents was collected, the range being 15 to 50 cc. Thus, morphine in the doses used consistently diminished the discharge of contents from the ileum.

*Effect on the Motility of the Human Ileum of the Intramuscular Injection of One and Two Milligram Doses of Dilaudid Hydrochloride.*—In 9 experiments the injection of 1 or 2 mg. of dilaudid hydrochloride caused the same type of response in the ileum as was obtained with morphine. One milligram of the drug appeared to have the same effect as 8 to 10 mg. of morphine sulfate. On 3 occasions when 2 mg. of dilaudid hydrochloride was administered the patient became nauseated, the nausea culminating in emesis once.

Dilaudid caused a decrease in the amount of contents discharged into the ileostomy bag. The amount collected ranged from 24 to 47.6 cc. for the three hour period, the average being 31 cc.

#### COLON

*Effect on the Motility of the Human Colon of the Intramuscular Injection of Five, Eight, Ten and Sixteen Milligram Doses of Morphine Sulfate.*—The patients evacuated the distal portion of the colon by enema each morning after breakfast. Normally no further material was passed until lavage the next morning. Thirty-three experiments of three hours' duration were performed in which morphine sulfate was administered in doses of 8, 10 and 16 mg. to these patients, who weighed from 160 to 190 pounds (72.6 to 86.2 Kg.). A twenty to forty minute control record was made before the drug was given. The records of these experiments were compared with those of 67 control periods of three hours' duration. The total motility and the propulsive motility were measured by a method described previously.<sup>10</sup> Effective propulsive activity was evidenced by the outward passage of the tube or tubes or by the passage of gas and fecal material.

In 25 of the 33 experiments an increase in tone occurred five to nine minutes after the injection. Type I contractions (fig. 2 C) at a rate of three to eight per minute were superimposed on the high tone. In 9 experiments a definite decrease in tone occurred in one of the particular segments under observation (fig. 2 D). (The waves seen in figure 2 D are not due to respiration, but are type I waves superimposed on low tone.) No relation was noted between the tone and the motility existing at the time of injection of morphine and the type of motor response elicited by the drug.

10. Borkon, E. L., and Templeton, R. D.: The Influence of Oil Enemas on Colon Motility in the Dog, *Am. J. Physiol.* **118**:775, 1937.

In 7 experiments 5 mg. of morphine sulfate was administered. As in the study of the ileum, this dose was not sufficient to cause the typical response observed after larger doses. A fairly typical response occurred in only 4 experiments; in 3 others the change in motility was not definite.

The data on the total motility and the propulsive motility are shown in the table. It is to be noted that after the administration of 8, 10 and 16 mg. of morphine sulfate the average total motility is decidedly increased, whereas the propulsive motility is decreased.

The most constant effect of the drug, other than an increase in the tone of the segment of the colon being studied, was a marked decrease in the propulsive motility. After the administration of morphine no fecal material was expelled. This was dramatically manifested on 9 occasions during the course of our studies when the patients reported for

*Quantitative Data Pertaining to the Action of Morphine, Dilaudid and Atropine on the Human Colon*

No. of Tests on Four Subjects	Substance Administered	Total Motility,* 50 Min. Periods			Propulsive Motility,† 50 Min. Periods		
		1	2	3	1	2	3
67	Control.....	53	57	50	13	10.5	7.5
33	8, 10 and 16 mg. of morphine sulfate.....	87	91	89.4	3.1	2.4	3.8
16	2 mg. of dilaudid hydrochloride.....	86	85	85.5	4.1	2.3	4.3
10	0.7 and 0.8 mg. of atropine sulfate.....	34	27.6	35.5	2.8	3.2	3.6
6	8 mg. of morphine sulfate and 0.7 mg. of atropine sulfate.....	64	69.3	68.4	2.0	1.8	2.3

\* Total motility, the percentage of the 50 minute experimental period during which the colon is active.

† Propulsive motility, a percentage of the total motility.

study with hypermotility of the colon of unknown cause except in 1 instance of overindulgence in alcohol. On these occasions fluid material was being intermittently and copiously discharged from the fistula with type II contractions of high amplitude. The administration of morphine completely abolished the discharge, not by reducing the quantity of motility, but by increasing the nonpropulsive motility and decreasing markedly the propulsive type of motility.

*Effect on the Motility of the Human Colon of the Intramuscular Injection of Two Milligrams of Dilaudid Hydrochloride.*—Sixteen experiments were performed. In 13 the tone of the segment of the colon being studied was decidedly increased; in 3 it was decreased. Figure 2 B illustrates the usual effect of 2 mg. of dilaudid hydrochloride. As in the case of a dose of 8 to 16 mg. of morphine sulfate, 2 mg. of dilaudid hydrochloride increased the tone of the colon and the amplitude of the type I nonpropulsive contractions. Thus, 2 mg. of dilaudid hydro-

chloride had approximately the same effect on the colon as 8 to 16 mg. of morphine sulfate. The quantitative data are shown in the table.

*Effect on the Motility of the Human Colon of the Subcutaneous Injection of Seven-Tenths and Eight-Tenths Milligram Doses of Atropine Sulfate.*—We administered atropine in ordinary therapeutic doses to our subjects primarily as a control for the group of experiments on atropine-morphine antagonism. However, we were also interested in the use of such doses because Cushny<sup>11</sup> and Bastedo<sup>12</sup> have stated on questionable grounds that atropine is practically without effect on the movements of the colon.

The dose of atropine used caused some drying of the mouth in our 4 patients. This fact was elicited by questioning and was not a spontaneous complaint. The spontaneous motility of the colon was diminished in all 4 subjects. It was completely abolished in 5 tests. In 3 other tests the amplitude and duration of the movements were decreased, and the quiescent periods were lengthened. In the 2 other tests only mild nonpropulsive activity was present. The average results are shown in the table.

It should be pointed out that with the multiple balloon technic it has been observed that in the dog atropine affects some segments of the colon more definitely than other segments.<sup>6b</sup> The distal portion of a dog's colon is more sensitive to the motor inhibitory action of atropine than is the proximal portion. These observations have to be considered in the interpretation of results for the human colon obtained with the use of a single balloon.

*Effect of Morphine-Atropine Antagonism on the Human Colon.*—In a previous study on the dog two of us (H. F. A. and A. C. I.) found that 1 mg. of atropine sulfate (0.028 to 0.052 mg. per kilogram of body weight) will antagonize the effect of 4 mg. of morphine sulfate on the colon.<sup>6b</sup> In the present study we have determined whether atropine antagonizes any of the stimulating effects of morphine on the colon of man.

In 6 three hour experiments on the 4 patients 0.7 mg. of atropine sulfate was given with 8 mg. of morphine sulfate. Other experiments were not performed because the results were consistent and correlated well with the results obtained on the dogs. Larger doses of atropine were not used, as was done in the case of the dogs, because of the disagreeable effects.

11. Cushny, A. R.: *A Textbook of Pharmacology and Therapeutics*, ed. 11, Philadelphia, Lea & Febiger, 1936.

12. Bastedo, W. A.: *The Value of Atropine and Belladonna in Stomach Disorders*, J. A. M. A. **106**:85 (Jan. 11) 1936.

The atropine antagonized definitely, though not completely, the stimulatory effect of morphine on the tone and the type I motility. The average results are shown in the table. As might be expected, the atropine tended to augment the inhibitory effect of morphine on propulsive motility.

#### COMMENT

Numerous studies on the effect of morphine on the human ileum and colon have been conducted. The characteristic feature of these studies is that more than 1 experiment on each subject has rarely been made and evidence of a quantitative nature is lacking. This we believe is the chief reason for the differences in opinion regarding the effect of morphine on the small intestine and colon of man. Another reason is the fact that any two segments of the colon do not necessarily react identically to a drug and that many authors do not distinguish between nonpropulsive and propulsive activity. This distinction cannot be made by balloon records alone. Some do not consider the fact that spontaneous changes in the type of motility occur. Unless one has control records for the same subject made over a relatively prolonged period under controlled dietary and other conditions in which no experimental variation is introduced, errors in interpretation are likely to result. In our studies, which were preceded by similar studies on the dog, the foregoing factors have been considered and quantitative data are provided.

*Ileum.*—In regard to the effect of morphine and dilaudid on the ileum of our subject, the administration of 8, 10 and 16 mg. doses of morphine sulfate or dilaudid hydrochloride in doses of 1 or 2 mg. definitely increased the tone and the nonpropulsive motility of the ileum.

These drugs definitely reduced the discharge of intestinal contents from the opening created by ileostomy over a three hour period of observation. The interpretation of what constitutes an effective peristaltic movement is the only real difference between our observations and those of Plant and Miller,<sup>1</sup> Abbott and Pendergrass,<sup>2a</sup> Yonkman, Hiebert and Singh<sup>3b</sup> and Puestow,<sup>13</sup> whose articles adequately reviewed the literature (see also Krueger<sup>14</sup> and Orr and Carlson<sup>3a</sup>). We believe that one cannot objectively determine whether a movement of the bowel is effectively peristaltic by a balloon record. To determine whether a movement represents effective peristalsis, we believe its push or pull, as demonstrated elsewhere,<sup>15</sup> or the propulsion of contents must occur and be measured.

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13. Puestow, C. B.: Intestinal Motility of Dog and Man, in Illinois Medical and Dental Monographs, Urbana, University of Illinois Press, 1940, vol. 2, no. 2.

14. Krueger, H.: The Action of Morphine on the Digestive Tract, *Physiol. Rev.* **17**:618, 1937.

15. Adler and Ivy.<sup>6b</sup> Cushny.<sup>11</sup>

On the basis of our motility records supported by the actual measurement of contents expelled from the ileostomy with and without morphine, it is evident that morphine increased ileal passage time, or "constipated" the ileum, in our subject in the presence of an increase in tone and nonpropulsive movements. The fact that churning movements may occur and produce borborygmi is evidence of increased activity but not evidence of increased rate of propulsion along the bowel. This is confirmatory of the roentgenologic observations of Abbott and Pendergrass,<sup>2a</sup> who observed a long delay in the time of passage from the intestine to the cecum and of the clearance of barium sulfate from the intestine after morphine was given. The pooling of barium sulfate in certain segments separated by nonfilled segments, or a "sausage string" effect, is compatible with the presence of increased tone and amplitude of nonpropulsive movements and the fact that all segments are not similarly affected by a drug at the same time. If the contents are not propelled, it is natural for pooling to occur with churning, provided one segment is more tonic than another. Synergistic or coordinated activity between segments would seem to be necessary for effective propulsion of contents. This type of activity is apparently embarrassed by the effect of morphine on the small intestine. Our interpretation of our own observations and of those of other investigators is that morphine produces dyskinesia or an imbalance between the nonpropulsive and the propulsive movements of the small intestine by increasing the nonpropulsive activity. Whether the drug acts directly on the intestine to augment nonpropulsive activity and to depress propulsive activity or whether it only augments nonpropulsive movement, which in turn depresses propulsive activity, is uncertain.

*Colon.*—The injection of ordinary therapeutic doses (6 to 16 mg.) of morphine sulfate, as almost every one agrees who has made single injections, causes an increase in the tone and the rhythmic movements of the colon. However, Pancoast and Hopkins,<sup>4b</sup> using the fluoroscope, observed variable results. Puestow,<sup>13</sup> who studied by inspection the everted cecum of a patient, observed only relaxation and local rhythmic waves. That this is rather unusual is shown by the graphically recorded results of Yonkman and associates,<sup>3b</sup> who observed that the injection of morphine was followed by an increase in the tone and the activity of the cecum of 3 patients who had undergone cecostomy. No one has apparently observed a relaxation of the distal portion of the colon of man after the administration of morphine. However, in 9 of 33 tests we observed relaxation in one of the segments of the descending colon being studied. The 9 instances of relaxation did not occur in any 1 subject and were unrelated to the type of motility present at the time of injection.

The fact, which is clearly evident in the colon of the dog when it is studied by the multiple balloon technic, that all segments of the colon do not respond alike at the same time to a drug might explain the relaxation observed by Puestow and the variable response reported by Pancoast and Hopkins (see the preceding paragraph). The fact that relaxation or loss of tone may occur in one segment during a period of ten or twenty minutes in which an adjacent segment may show an increase in tone in response to morphine indicates that the pooling of barium sulfate, or the "sausage string effect," noted in the small intestine by Abbott and in the colon by Jackman and Bargaen<sup>16</sup> may be due to an actual relaxation of the segment. This relaxation may be due to the direct effect of morphine on the segment or to a reflex effect from the adjacent hypertonic segment. This evidence of dyskinesia of the colon along with the definite decrease in propulsive activity, as revealed by our balloon records and by the lack of expulsion of contents from the opening created by colostomy, is sufficient to account for the delayed passage of barium sulfate through the colon after the administration of morphine (Krueger<sup>14</sup>).

The effect of atropine in decreasing the tone and the motility of the colon of man confirms the observations of Elsom and Drossner<sup>17</sup> and Jackman and Bargaen.<sup>16</sup> This effect is further substantiated by the observation that on the average a dose of atropine sufficient to cause dryness of the mouth partially antagonizes the increase in tone and in nonpropulsive motility of the colon caused by morphine. This provides experimental justification for the simultaneous use of the two drugs for pain originating from the alimentary tract.

The fact that atropine and other antispasmodics we have used to date in reasonable doses (experiments in progress) do not completely abolish the hypertonus caused by morphine indicates to us the reason why none of them is completely satisfactory. In our opinion, the ideal antispasmodic is yet to be discovered. We suspect that when it is discovered, it will completely annul the increase in tone and in nonpropulsive activity induced by morphine.

#### SUMMARY AND CONCLUSIONS

Morphine sulfate in doses of 8, 10 and 16 mg. administered intramuscularly to a 140 pound (63.5 Kg.) healthy male patient who had undergone an ileostomy usually increased the tone and the amplitude of the nonpropulsive type of rhythmic contractions of the segments of the

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16. Jackman, R. J., and Bargaen, J. A.: The Influence of Certain Antispasmodic Drugs on the Intestine of Man, *Surg., Gynec. & Obst.* **67**:63, 1938.

17. Elsom, K. A., and Drossner, J. L.: Intubation Studies of the Human Small Intestine: XVII. The Effect of Atropine and Belladonna on the Motor Activity of the Small Intestine and Colon, *Am. J. Digest. Dis.* **6**:589, 1939.

distal portion of the ileum studied. The propulsive activity of the ileum was uniformly decreased; this was shown by the motility records and by the definite decrease in the amount of contents discharged into the ileostomy bag during a three hour period.

Dilaudid hydrochloride in doses of 1 or 2 mg. administered intramuscularly had a similar effect.

Morphine sulfate in doses of 8, 10 and 16 mg. administered intramuscularly to 4 healthy male patients who had undergone colostomy with resection of the proximal portion of the sigmoid and who weighed from 140 to 190 pounds (72.6 to 86.2 Kg.) usually increased the tone and the amplitude of the nonpropulsive type of rhythmic contractions of the segments of the descending colon studied. In all of 40 tests in which 5 to 16 mg. of the drug was given the propulsive motility of the descending colon was diminished or abolished. On 9 occasions in which the colon was manifesting diarrhea the administration of morphine abolished the discharge by decreasing the propulsive type of motility and not by reducing the tone and the quantity of motility the segments manifested.

Atropine sulfate in doses of 0.7 to 0.8 mg. administered intramuscularly to the 4 subjects just mentioned usually decreased the total motility of the portion of the colon being studied; the propulsive motility was uniformly diminished.

The administration of atropine sulfate (0.7 mg.) antagonizes partially that effect of morphine sulfate (8 mg.) which causes an increase in tone and in nonpropulsive motility. This evidence, we believe, supports the combined use of the drugs in the treatment of severe gastrointestinal pain. The failure of atropine in ordinary doses to antagonize completely the increase in tone and in nonpropulsive motility usually induced by morphine is interpreted as indicating why atropine is not always as effective an antispasmodic as is desired clinically.

Morphine sulfate delays the ileal and colonic passage time of material in man, primarily by interfering with or diminishing propulsive motility. We suggest that morphine causes dyskinesia of the small and large intestine. Adjacent segments of bowel must be coordinated in order that effective propulsion may occur.<sup>7</sup>



# QUANTITATIVE STUDIES OF DIRECT-REACTING SERUM BILIRUBIN

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AND

G. HOLLANDER, M.D.

PHILADELPHIA

In the presence of hyperbilirubinemia little or no clinical significance is usually attached at the present time to the nature of the qualitative van den Bergh reaction, except in the diagnosis of hemolytic forms of jaundice. Its specificity even in this connection is rendered questionable by the recent reports by Dameshek and Singer<sup>1</sup> of instances of non-hemolytic familial jaundice (serum bilirubin values up to 13.1 mg. per hundred cubic centimeters) and by Malloy and Lowenstein<sup>2</sup> of apparently nonhemolytic hereditary jaundice in rats, only the indirect van den Bergh reaction having been obtained by these authors. Although the factors which determine the difference between the direct and the indirect reaction are not definitely known, it seems safe to assume for clinical purposes that bilirubin in the serum which does not give the direct reaction has not passed through the hepatic cells and that which does give this reaction has been reabsorbed into the blood from the bile canaliculi. This relation of the liver to the nature of the van den Bergh reaction was demonstrated clearly by Bollman and Mann,<sup>3</sup> who found in dogs that after cholecystectomy and ligation of the common bile duct practically all of the serum bilirubin was of the direct-reacting variety, increasing in amount with the time after operation. Subsequent hepatectomy, regardless of the level of serum bilirubin, was followed by a continued rise in the indirect-reacting serum bilirubin, but the direct-

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1. Dameshek, W., and Singer, K.: Familial Nonhemolytic Jaundice, *Arch. Int. Med.* **67**:259 (Feb.) 1941.

2. Malloy, H. T., and Lowenstein, L.: Hereditary Jaundice in Rat, *Canad. M. A. J.* **42**:122, 1940.

3. Bollman, J. L., and Mann, F. C.: Studies of the Physiology of the Liver: XXII. The van den Bergh Reaction in the Jaundice Following Complete Removal of the Liver, *Arch. Surg.* **24**:675 (Jan.) 1932.

reacting bilirubin remained at the same concentration it had reached as a result of the biliary obstruction and did not increase after removal of the liver.

Instances are occasionally observed clinically of mild grades of hyperbilirubinemia with a negative direct van den Bergh reaction in the absence of evidences of excessive hemolysis and, less frequently, of a positive direct reaction in the presence of a normal concentration of serum bilirubin. These phenomena occur most commonly in cases of nonobstructive cirrhosis, mild hepatitis and congestive heart failure and in the early stages of bile stasis and late stages of biliary decompression. Investigation of the absolute concentrations of direct-reacting and indirect-reacting bilirubin in the serum in such disorders has been hampered by the inaccuracy of hitherto available quantitative methods. The introduction, by Malloy and Evelyn,<sup>4</sup> of a photoelectric method for the exact determination of total and "direct" bilirubin has raised the possibility that some light might be thrown on the pathogenesis of these phenomena.

The present report consists of quantitative determinations of total (indirect-reacting) and direct-reacting serum bilirubin in 35 normal subjects, 94 patients with hepatitis (172 determinations), 14 with non-obstructive hepatic cirrhosis (41 determinations), 36 with extrahepatic biliary obstruction of varying degree (75 determinations), 11 with congestive heart failure and either hyperbilirubinemia or some other manifestation of impaired hepatic function (18 determinations) and 18 with hyperbilirubinemia due to other causes (40 determinations). Bilirubin was determined by the method of Malloy and Evelyn,<sup>4</sup> readings of "direct" bilirubin being made at thirty minutes in all cases and at five minutes in some cases. The latter (five minute) readings have been reported elsewhere<sup>5</sup> and, having been found to be of no added significance, will not be presented here.

## RESULTS

The range of findings in each group of subjects in the series is presented in table 1.

*Normal Subjects.*—The concentration of serum bilirubin was 0.1 to 0.8 mg. per hundred cubic centimeters, the direct-reacting bilirubin constituting 0 to 75 per cent of the total bilirubin. As indicated in figure 1, it was absent in only 3 instances and was present in every case

4. Malloy, H. T., and Evelyn, K. A.: The Determination of Bilirubin with the Photoelectric Colorimeter, *J. Biol. Chem.* **119**:481, 1937.

5. Cantarow, A.; Wirts, C. W., Jr., and Hollander, G.: Quantitative Studies of Direct Serum Bilirubin, *Proc. Soc. Exper. Biol. & Med.* **45**:253, 1940.

in which the concentration of total serum bilirubin exceeded 0.2 mg. per hundred cubic centimeters. With increasing values for the total serum bilirubin, the maximum percentage of the total represented by direct-reacting bilirubin diminished steadily from a peak of 75 per cent at 0.2 mg. per hundred cubic centimeters to 44 per cent at 0.8 mg. per hundred cubic centimeters.

*Patients with Cirrhosis.*—The individual values obtained in patients with cirrhosis are presented in figure 2. In all of 17 instances in this group in which the concentration of total serum bilirubin was within normal limits, the proportion of direct-reacting bilirubin (67 to 100 per

TABLE 1.—Percentage of Direct-Reacting Bilirubin in the Serum at Different Levels of Total Serum Bilirubin

Total Bilirubin, Mg./100 Cc.	Direct-Reacting Bilirubin, 30 Min. Readings, %					
	Normal	Cirrhosis	Hepatitis	Obstruction	Poisoning Caused by Sulfanilamide or One of Its Derivatives	Congestive Heart Failure
0.1	0-50	.....	.....	.....	.....	.....
0.2	0-75	.....	100	.....	.....	.....
0.3	33-67	.....	.....	.....	.....	.....
0.4	25-62	100	75	.....	50	.....
0.5	40-60	70-100	40-100	.....	.....	.....
0.6	33-50	67-83	83	.....	44	.....
0.7	36-50	.....	57-100	.....	.....	27
0.8	44	75-100	37-75	.....	62-75	.....
0.81- 1.0	.....	60-70	44-80	56	44-70	33-55
1.1 - 2.0	.....	33-86	25-100	38-75	33-79	30-61
2.1 - 5.0	.....	84-100	19-85	59-76	11-67	26-57
5.1 -10.0	.....	31-69	51-88	50-88	8-38	.....
10.1 -20.0	.....	.....	59-88	60-93	.....	.....
20.1 plus	.....	.....	84	66-92	.....	.....

cent) exceeded that present in normal subjects at the same level of total bilirubin (fig. 1). In the patients with hyperbilirubinemia, direct-reacting bilirubin comprised 60 per cent or more of the total in 19 of 24 instances.

*Patients with Hepatitis.*—The data on patients with hepatitis are presented in figure 3. In 19 of 23 instances in which the total serum bilirubin was within normal limits, the proportion of direct-reacting bilirubin exceeded that in normal subjects at the same level of total bilirubin (fig. 1). The degree of variation in the proportion of direct-reacting bilirubin lessened somewhat with increasing concentrations of total serum bilirubin, chiefly because of a gradual rise in the level of minimum values (table 1 and fig. 3). Direct-reacting bilirubin com-

prised 60 per cent or more of the total bilirubin in 35 of 53 instances (66 per cent) of concentrations of total serum bilirubin of 1.1 to 2.0 mg. per hundred cubic centimeters, in 32 of 50 instances (64 per cent) of concentrations of 2.1 to 5 mg. per hundred cubic centimeters, in 22 of

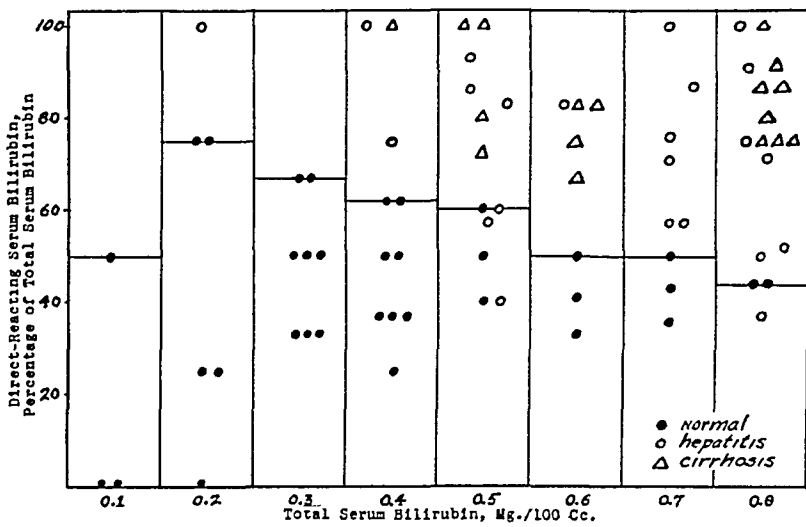


Fig. 1.—Proportion of direct-reacting serum bilirubin at normal levels of total serum bilirubin in normal subjects and in patients with hepatitis and with cirrhosis.

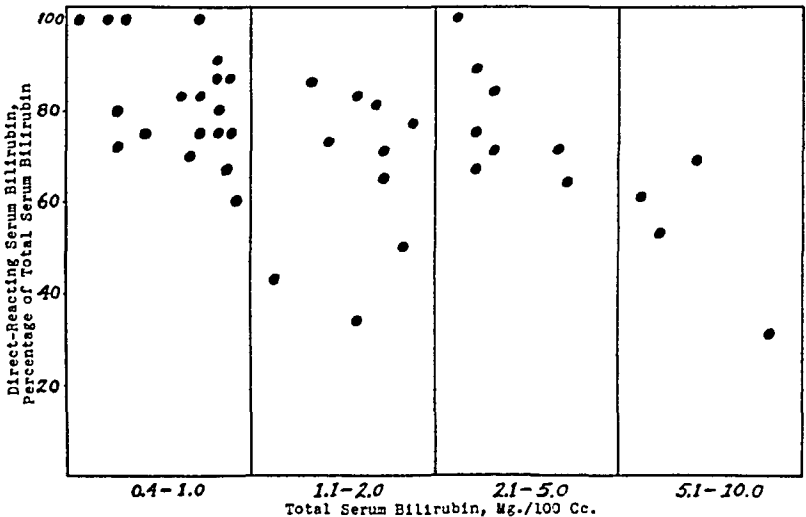


Fig. 2.—Proportion of direct-reacting bilirubin in the serum of patients with cirrhosis.

27 instances (81 per cent) of concentrations of 5.1 to 10 mg. per hundred cubic centimeters and in 14 of 15 instances (93 per cent) of concentrations above 10 mg. per hundred cubic centimeters.

*Patients with Extrahepatic Obstruction.*—The data on this group of patients, presented in detail in figure 4, were obtained during periods

of increasing, sustained and decreasing bile stasis, in the presence both of complete and of incomplete obstruction of the common bile duct. Direct-reacting bilirubin comprised 60 per cent or more of the total bilirubin in 3 of 7 instances (43 per cent) of concentrations of total

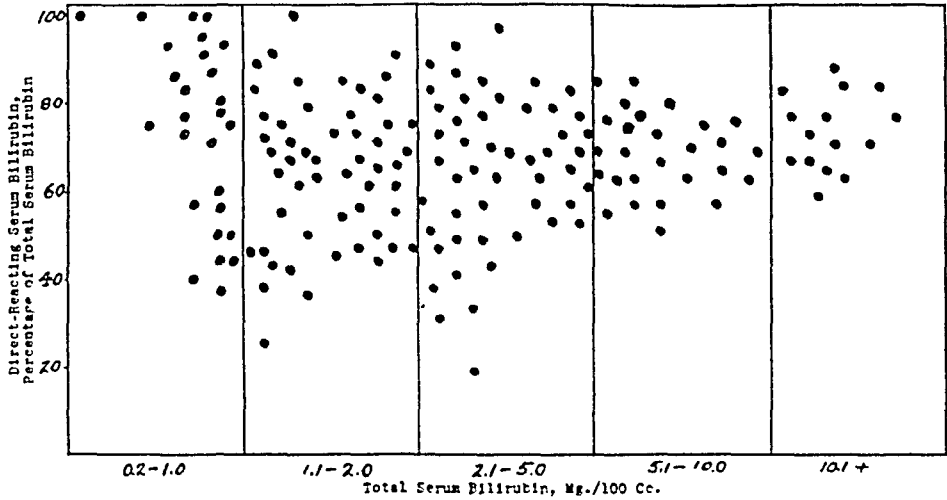


Fig. 3.—Proportion of direct-reacting bilirubin in the serum of patients with hepatitis.

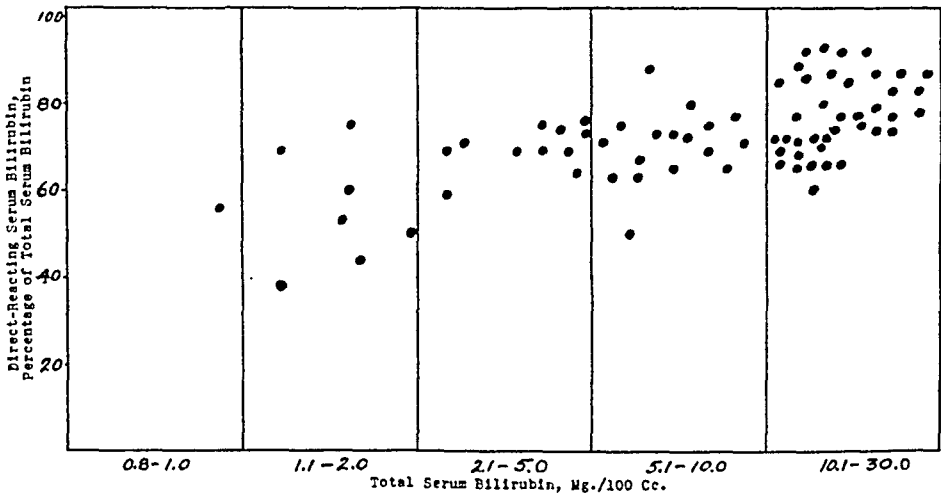


Fig. 4.—Proportion of direct-reacting bilirubin in the serum of patients with biliary obstruction.

serum bilirubin of 1.1 to 2 mg. per hundred cubic centimeters, in 10 of 11 instances (91 per cent) of concentrations of 2.1 to 5 mg. per hundred cubic centimeters, in 16 of 17 instances (94 per cent) of concentrations of 5.1 to 10 mg. per hundred cubic centimeters and in

all of 39 instances (100 per cent) of concentrations above 10 mg. per hundred cubic centimeters.

*Patients with Congestive Heart Failure.*—The data obtained on these patients are presented in figure 5. Hyperbilirubinemia (above 0.8 mg. per hundred cubic centimeters) was present in 17 of the 18 instances,

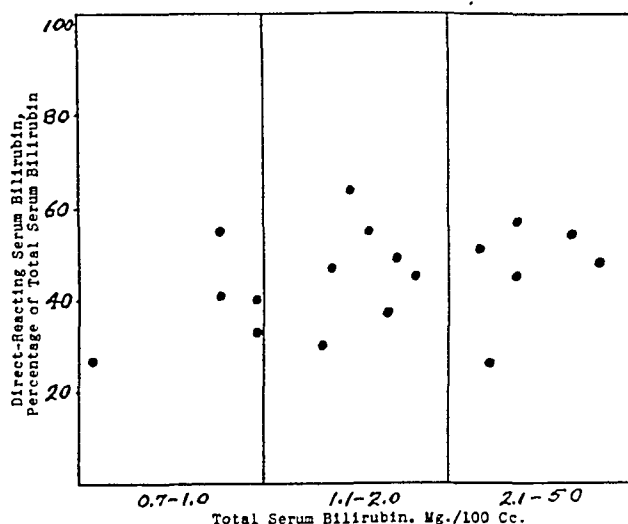


Fig. 5.—Proportion of direct-reacting bilirubin in the serum of patients with congestive heart failure and impairment of hepatic function.

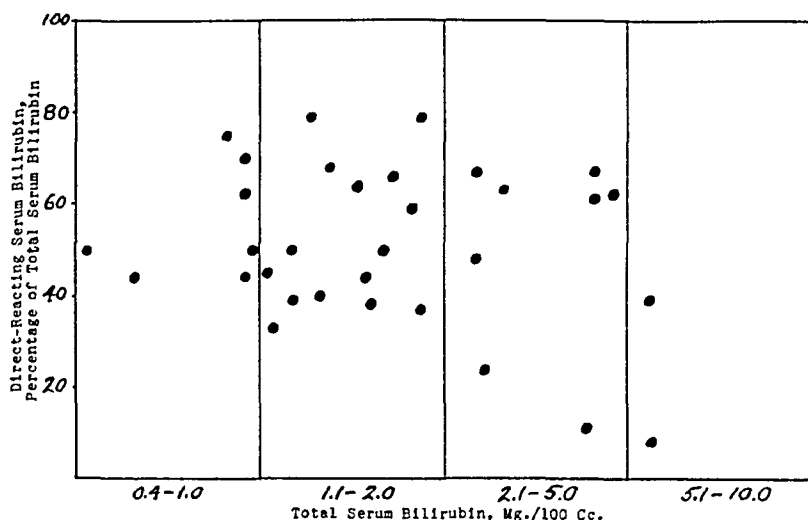


Fig. 6.—Proportion of direct-reacting bilirubin in the serum of patients following the administration of sulfanilamide or one of its derivatives.

and the proportion of direct-reacting bilirubin was above 60 per cent in only 1 case.

*Patients Treated with Sulfanilamide or One of Its Derivatives.*—The data obtained on patients in this group are presented in figure 6. Hyperbilirubinemia was present in 28 of the 32 determinations. The proportion

of direct-reacting bilirubin exceeded 60 per cent in 5 of 15 instances (33 per cent) of concentrations of total serum bilirubin of 1.1 to 2 mg. per hundred cubic centimeters, in 5 of 8 instances (62 per cent) of concentrations of 2.1 to 5 mg. per hundred cubic centimeters and in neither of 2 instances of concentrations above 5 mg. per hundred cubic centimeters. Serial data obtained on 1 patient are presented in table 2.

TABLE 2.—*Jaundice Following Treatment with Sulfanilamide*

	Days of Observation							
	1	3	4	5	6	8	10	12
Total serum bilirubin, mg./100 cc. ....	5.9	4.6	2.9	1.6	1.1	0.8	1.0	0.4
Direct-reacting bilirubin, 30 min. reading, mg./								
100 cc. ....	0.5	0.5	0.7	0.8	0.5	0.5	0.5	0.2
Direct van den Bergh reaction.....	—	—	+	+	+	+	+	—

*Patients with Miscellaneous Conditions.*—Data obtained on 5 patients with pernicious anemia are tabulated as follows:

Patient No.	Total Serum Bilirubin, Mg./100 Cc.	Direct-Reacting Serum Bilirubin, %
1.....	1.2	46
2.....	1.0	60
3.....	1.0	60
4.....	0.9	67
5.....	0.9	44

In 1 patient with massive hemorrhage from a duodenal ulcer the direct-reacting serum bilirubin comprised 33 per cent of the total of 0.9 mg. of bilirubin per hundred cubic centimeters of serum. In 2 patients with congenital hemolytic jaundice the direct-reacting serum bilirubin was 3 per cent of a total of 9.5 mg. per hundred cubic centimeters and 14 per cent of a total of 1.4 mg. per hundred cubic centimeters, respectively.

*Direct-Reacting Bilirubin and Direct van den Bergh Reaction.*—In the patients with cirrhosis, biliary obstruction and congestive heart failure, the direct van den Bergh reaction was negative in the presence of hyperbilirubinemia (above 0.8 mg. per hundred cubic centimeters) on 30 occasions and was positive in the presence of normal concentrations of total serum bilirubin in 17 instances. These data are presented in table 3. A negative direct van den Bergh reaction was obtained with concentrations of total serum bilirubin as high as 2.2 mg. per hundred cubic centimeters, the direct-reacting bilirubin being 0.6 mg. per hundred cubic centimeters, or 27 per cent of the total (hepatitis), and with concentrations of direct-reacting bilirubin as high as 1.1 mg. per hundred cubic centimeters, comprising 69 per cent of the total of 1.6 mg. per

hundred cubic centimeters (hepatitis). A positive direct van den Bergh reaction was obtained with concentrations of total serum bilirubin as low as 0.4 mg. per hundred cubic centimeters, all of which was direct-reacting bilirubin (cirrhosis) and with concentrations of direct-reacting bilirubin as low as 0.3 mg. per hundred cubic centimeters, comprising 37 per cent of the total of 0.8 mg. per hundred cubic centimeters (hepatitis).

TABLE 3.—*Relation of Qualitative van den Bergh Reaction to Amount and Proportion of Direct-Reacting Bilirubin in the Serum*

Direct van den Bergh Reac- tion	Total Serum Bili- rubin, Mg./ 100 Cc.	Direct-Reacting Bilirubin, 30 Min. Reading							
		Hepatitis		Cirrhosis		Obstruction		Congestive Heart Failure	
		Mg./ 100 Cc.	%	Mg./ 100 Cc.	%	Mg./ 100 Cc.	%	Mg./ 100 Cc.	%
Positive	0.4	...	..	0.4	100	...	..	...	..
	0.5	...	..	0.5	100	...	..	...	..
	0.5	...	..	0.4	70	...	..	...	..
	0.6	0.5	83	0.4	67	...	..	...	..
	0.7	0.4	57	0.5	83	0.5	71	...	..
	0.7	0.6	86	...	...	0.5	71	...	..
	0.7	0.6	86	...	...	...	..	...	..
	0.8	0.3	37	0.6	75	0.8	100	...	..
	0.8	0.4	50	0.8	100	...	..	...	..
	0.8	0.6	75	...	...	...	..	...	..
Negative	0.9	0.4	44	...	...	0.5	56	0.3	33
	0.9	0.4	44	...	...	...	..	0.5	55
	0.9	0.7	78	...	...	...	..	...	..
	1.0	0.5	50	...	...	0.8	80	0.4	40
	1.0	0.5	50	...	...	...	..	...	..
	1.0	0.6	60	...	...	...	..	...	..
	1.1	0.4	36	...	...	...	..	...	..
	1.1	0.6	54	...	...	...	..	...	..
	1.2	0.3	25	0.8	67	...	..	...	..
	1.2	0.5	42	...	...	...	..	...	..
	1.2	0.5	42	...	...	...	..	...	..
	1.3	0.5	38	0.7	54	...	..	...	..
	1.3	0.6	46	...	...	...	..	...	..
	1.4	0.6	43	0.6	43	...	..	...	..
	1.4	0.7	50	...	...	...	..	...	..
	1.4	0.7	50	...	...	...	..	...	..
	1.5	0.7	47	...	...	0.8	53	...	..
	1.5	...	..	...	...	0.9	60	...	..
	1.6	1.1	69	0.9	56	...	..	...	..
	2.2	0.6	27	...	...	...	..	...	..

COMMENT

The data reported here for normal subjects are in essential agreement with the observation of Malloy and Evelyn<sup>6</sup> that "direct" bilirubin comprises about 35 to 70 per cent of the total serum bilirubin of normal adults. It appears, however, on the basis of a limited number of observations, that the proportion of the former decreases from a peak

6. Malloy, H. T., and Evelyn, K. A., cited by Waugh, T. R.; Merchant, F. T., and Maughan, G. B.: Blood Studies on the Newborn: II. Direct and Total Blood Bilirubin Determinations Over a Nine-Day Period, with Special Reference to Icterus Neonatorum, Am. J. M. Sc. **199**:9, 1940.



of 75 to about 44 per cent of the total at increasing levels of total bilirubin within normal limits (0.2 to 0.8 mg. per hundred cubic centimeters), the maximum concentration of "direct" bilirubin increasing simultaneously from 0.15 to 0.352 mg. per hundred cubic centimeters. The significance of the presence in normal serum of such relatively large quantities of bilirubin giving the van den Bergh reaction in aqueous acid (direct reaction) cannot be established because of the present uncertainty regarding the factors responsible for the difference in behavior of "direct" and of "indirect" bilirubin. It is obvious that production of the qualitative direct reaction, at least in serums of relatively low bilirubin content, is not determined by the concentration of direct-reacting bilirubin or by the proportion which it constitutes of the total. It must be remembered, however, that readings of the qualitative reaction are made at thirty seconds, while those of the quantitative reactions are made at thirty minutes, which may be responsible, in part at least, for this discrepancy. Nevertheless, it is difficult to explain a change such as that observed in a patient after administration of sulfanilamide (table 2), namely, the transition from a negative to a positive direct van den Bergh reaction at the same level of "direct" bilirubin (0.5 mg. per hundred cubic centimeters), with a decreasing concentration of total bilirubin (5.9 to 0.8 mg. per hundred cubic centimeters).

In the patients with pernicious anemia the "direct" bilirubin ranged from 0.396 to 0.603 mg. per hundred cubic centimeters at levels of total serum bilirubin of 0.9 to 1.2 mg. per hundred cubic centimeters, the direct van den Bergh reaction being negative in each instance. These figures represent an increase in the former above the maximum observed in normal subjects (0.352 mg. per hundred cubic centimeters) and are in rather striking contrast to the relatively low values obtained in a patient with gastrointestinal hemorrhage (0.307 mg.) and in patients with congenital hemolytic jaundice (0.285 and 0.196 mg.).

Hyperbilirubinemia, even of minimal degree, in the patients with cirrhosis, hepatitis, biliary obstruction and congestive heart failure and in patients treated with sulfanilamide or one of its derivatives was accompanied by an abnormally high level of "direct" bilirubin in all patients but 1 with hepatitis (0.3 mg.), 1 with congestive heart failure (0.33 mg.) and 1 with sulfanilamide poisoning (0.31 mg.). Of particular significance is the fact that at levels of serum bilirubin within normal limits the concentration of "direct" bilirubin was above the maximum observed in normal subjects in all of the patients with cirrhosis and in 19 of 23 patients with hepatitis. The highest value for non-direct-reacting bilirubin in normal subjects was 0.448 mg. per hundred cubic centimeters. In the patients with hyperbilirubinemia, concentrations above this level

were present in all but 6 with cirrhosis (0.0 to 0.437 mg.), in all but 1 with biliary obstruction, in all with congestive heart failure and in all but 3 with poisoning caused by sulfanilamide or one of its derivatives. It is interesting that, in contrast to these findings, in about one half of the patients with hepatitis with concentrations of total serum bilirubin of 1.1 to 2 mg. per hundred cubic centimeters the level of non-direct-reacting bilirubin was within the limits of normal. The percentage of such levels decreased sharply at higher degrees of bilirubinemia, and with concentrations of total serum bilirubin above 4 mg. per hundred cubic centimeters there was an elevation of the non-direct-reacting pigment in every instance.

If the view can be maintained that bilirubin in the blood that does not give the direct van den Bergh reaction has not passed through the hepatic cells, while that which does give the reaction has been reabsorbed from hepatic cells or from the bile canaliculi, these data furnish interesting information regarding the pathogenesis of hyperbilirubinemia in the conditions represented in this series of patients. In the great majority of cases the jaundice is apparently a combination of the "regurgitation" and the "retention" variety, as designated by Rich.<sup>7</sup> It appears, also, that the regurgitation mechanism frequently predominates in those patients with cirrhosis or hepatitis with normal or slightly increased bilirubinemia. In jaundice due to congestive heart failure or to poisoning caused by sulfanilamide or one of its derivatives the increase in "indirect" bilirubin may be contributed to by increased production (excessive hemolysis). Other data must be taken into consideration if the role of this factor is to be evaluated properly.<sup>8</sup> The observations presented here suggest that the quantitative determination of "direct" serum bilirubin may be of clinical value in detecting hepatic functional impairment in the presence of a normal concentration of total bilirubin. Values above the maximum obtained in normal subjects (0.352 mg. per hundred cubic centimeters) or proportions of the total greater than those observed at different levels of normal bilirubinemia (fig. 1) are commonly present in patients with cirrhosis or mild grades of hepatitis.

#### SUMMARY

Determinations were made of the concentration of total and of "direct" bilirubin in the serum of normal subjects and of patients with cirrhosis, hepatitis, biliary obstruction, congestive heart failure and poisoning caused by sulfanilamide or one of its derivatives. The serum

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7. Rich, A. R.: The Pathogenesis of the Forms of Jaundice, *Bull. Johns Hopkins Hosp.* **47**:338, 1930.

8. Kugel, M. A., and Lichtman, S. S.: Factors Causing Clinical Jaundice in Heart Disease, *Arch. Int. Med.* **52**:16 (July) 1933.

of normal subjects contained 0 to 0.352 mg. of "direct" bilirubin per hundred cubic centimeters, the maximum proportion of the total serum bilirubin being 75 per cent when the latter was 0.2 mg. per hundred cubic centimeters and decreasing steadily to 44 per cent at a concentration of total bilirubin of 0.8 mg. per hundred cubic centimeters.

Data are presented which indicate that jaundice in the great majority of patients with cirrhosis, hepatitis, biliary obstruction and congestive heart failure is a combination of the "regurgitation" and the "retention" variety. They also suggest that the quantitative determination of "direct" serum bilirubin may be of clinical value in detecting hepatic functional impairment in the presence of a normal concentration of total serum bilirubin, particularly in patients with cirrhosis or mild grades of hepatitis.

# CARBOHYDRATE COMBUSTION IN HUMAN SUBJECTS AFTER ORAL AND AFTER INTRAVENOUS ADMINISTRATION OF DEXTROSE

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AND

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In some studies being carried on at the New England Deaconess Hospital on the metabolism of sugars in patients with diabetes mellitus, it has been observed occasionally that intravenous administration of dextrose is not followed by the expected rise in the respiratory quotient. As intravenous injection of dextrose is a common practice in medicine, particularly after surgical procedures, it was considered worth while to make a comparative study of the changes in the respiratory quotient and in the total metabolic rate of normal human subjects after oral ingestion and after intravenous administration of this sugar.

In 2 fasting rabbits given intravenous injections of dextrose (10 cc. of a 13 per cent solution in thirteen minutes and 50 cc. of a solution containing 6 Gm.—rate of injection not stated) Zuntz and von Mering<sup>1</sup> noted marked increases in the respiratory quotient. In another fasting rabbit, given by stomach tube 20 Gm. of dextrose in 80 cc. of water, they also observed an increase in the quotient. In a rabbit which had fasted twenty-two hours Wolfers<sup>2</sup> noted that an intravenous injection of a 5 per cent solution of dextrose (amount and rate not given) failed to cause an increase in the respiratory quotient, which he ascribed to the fact that the rabbit still had a good supply of carbohydrate in the body and hence a high initial quotient. In another rabbit, which had fasted forty-eight hours, he found that intravenous injection of a 5 per cent solution of dextrose (0.272 Gm. per fifteen minutes for one and three-quarters hours) caused an increase in the respiratory quotient.

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A preliminary report of this study was presented before the American Institute of Nutrition, New Orleans, March 13, 1940 (*J. Nutrition* [supp.] **19**:10, 1940).

From the George F. Baker Clinic (Dr. Elliott P. Joslin, Medical Director), New England Deaconess Hospital, and the Nutrition Laboratory, Carnegie Institution of Washington.

1. Zuntz and von Mering: Inwiefern beeinflusst Nahrungszufuhr die thierischen Oxydationsprocesse? *Arch. f. d. ges. Physiol.* **32**:173-221, 1883.

2. Wolfers, J.: Untersuchungen über den Einfluss einiger stickstofffreier Substanzen, speciell des Alkohols, auf den thierischen Stoffwechsel, *Arch. f. d. ges. Physiol.* **32**:222-279, 1883.

Laulanié<sup>3</sup> reported increases in the respiratory quotients of 2 fasting dogs given 10, 36 and 50 Gm. of dextrose intravenously in thirty minutes, ten minutes and one hour, respectively. After intravenous injection of dextrose at rates ranging from 1 to 9 Gm. per kilogram per hour and for periods lasting in some instances two to eight hours, increases in the respiratory quotients of dogs were also noted by Harley,<sup>4</sup> Woodyatt,<sup>5</sup> Boyd and associates,<sup>6</sup> Hines and co-workers,<sup>7</sup> Wierzuchowski<sup>8</sup> and Wierzuchowski and Sekuracki.<sup>9</sup> On the other hand, Wierzuchowski and Borkowski<sup>10</sup> observed a decrease in the respiratory quotient after the administration of dextrose by vein. Three human subjects (2 normal and 1 abnormal) studied by Bernstein and Falta<sup>11</sup> showed distinct rises in the respiratory quotient after intravenous injection of 30 or 35 Gm. of dextrose in 300 or 500 cc. of water (rate not given); their glycogen stores had been previously depleted. Koster and associates<sup>12</sup> and Collens and co-workers<sup>13</sup> reported that after intra-

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3. Laulanié, F.: Des renseignements fournis par les échanges respiratoires sur la destination immédiate des hydrates de carbone, *Arch. de physiol.* **28**:791-802, 1896.

4. Harley, V.: Influence du sucre en circulation sur les gaz de la respiration et sur la chaleur animale, *Arch. ital. de biol.* **21**:173-189, 1894.

5. Woodyatt, R. T.: Studies on Intermediate Carbohydrate Metabolism, in Harvey Lectures, 1915-1916, Philadelphia, J. B. Lippincott Company, 1916, pp.326-345.

6. Boyd, J. D.; Hines, H. M., and Leese, C. E.: Study of Response to Continuous Intravenous Injection of Large Amounts of Glucose, *Am. J. Physiol.* **74**: 656-673 (Nov.) 1925.

7. Hines, H. M.; Boyd, J. D., and Leese, C. E.: The Effect of Fasting upon Certain Phases of Carbohydrate Metabolism, *Am. J. Physiol.* **88**:240-244 (March) 1929.

8. Wierzuchowski, M.: Intermediärer Kohlenhydratstoffwechsel: VIII. Mitteilung. Respiratorischer Gaswechsel der Glykose, Fructose und Galaktose bei ihrer intravenösen Injektion, *Biochem. Ztschr.* **230**:187-224, 1931; Oxidation of Glucose as Function of Its Supply, *J. Physiol.* **90**:440-464 (Sept.) 1937; The Origin and Limits of the Specific Dynamic Action of Intravenous Glucose, *ibid.* **91**:140-171 (Nov.) 1937.

9. Wierzuchowski, M., and Sekuracki, F.: Spaltungs-, Oxydations- und Energieumsatz beim Hunde: I. Mitteilung. Bildung und Beseitigung der Milchsäure in den Organen beim Hungern, sowie während der Oxydation von Galaktose, Glucose und Maltose, *Biochem. Ztschr.* **276**:91-111, 1935.

10. Wierzuchowski, M., and Borkowski, Z.: Differentiation of the Forms of Glucose Intoxication, *Acta biol. exper.* **12**:168-173, 1938; abstracted, *Biol. Abstr.* **13**:14539, 1939.

11. Bernstein, S., and Falta, W.: Respiratorischer Stoffwechsel und Blutzuckerregulation, *Deutsches Arch. f. klin. Med.* **125**:233-283, 1918.

12. Koster, H.; Goldzieher, M.; Collens, W. S., and Gerber, I. E.: Studies on Lactic Acid in the Blood: I. The Effect of Glucose and Insulin, *J. Lab. & Clin. Med.* **15**:723-726 (May) 1930.

13. Collens, W. S.; Goldzieher, M., and Koster, H.: Untersuchungen zur Wirkungsweise intravenöser Traubenzuckerinjektionen, *Klin. Wchnschr.* **10**:582-586 (March 28) 1931.

venous injection of 250 cc. of dextrose in a 20 per cent solution there were increases in the respiratory quotients of nondiabetic patients before operation but no increase or only a slight increase in the quotients of such patients during the first week following operation, after which there was a marked increase. Jahn<sup>14</sup> gave 50 Gm. of dextrose in 200 cc. of water both by mouth and intravenously to a normal and a diabetic subject. After oral administration the respiratory quotient of the normal subject increased; unfortunately, the course of the quotient after the intravenous injection was not reported. In the diabetic subject the respiratory quotient decreased after administration of dextrose by both methods. Pijoan and Gibson<sup>15</sup> gave normal human subjects 50 cc. of a 50 per cent dextrose solution intravenously and observed insignificant increases in the respiratory quotient. Examination of the literature failed to reveal any observations on the same normal human subject in which the effects on the respiratory quotient of oral and of intravenous administration of dextrose were compared.

#### METHOD

Four normal men, students of a nearby university, were used as subjects. The respiratory exchange was measured with an open circuit helmet apparatus involving gas analysis.<sup>16</sup> The gas analysis apparatus was standardized during the two months' period of study by nine analyses of outdoor air, which gave an average value for carbon dioxide content of 0.033 per cent, with a standard deviation of 0.0015 and an average value for oxygen content of 20.938 per cent, with a standard deviation of 0.0043. In four alcohol control tests the apparatus showed respiratory quotients of 0.661, 0.662, 0.670 and 0.674. The respiratory exchange was measured for three consecutive ten minute base line periods after the usual half hour of rest, with the subject sitting, postabsorptive. The sugar was then given orally or intravenously, according to the program, and the exchange was measured for nine consecutive fifteen minute periods after the administration of the sugar. When the dextrose was taken by mouth, 50 Gm. was given in 300 cc. of water, and an additional 50 cc. of water was used for a rinse. The temperatures of the doses varied from 9.5 to 18.5 C. The subject drank the solution within three to ten minutes, and about fifteen to twenty minutes after he finished, the first period of measurement following ingestion of the sugar began. When the sugar was administered intravenously, 50 Gm. was given in 500 cc. of physiologic solution of sodium chloride. The injection, in an antecubital vein, began four to nine minutes before the first period of measurement after the sugar was given. The duration of injection was about twenty to twenty-eight minutes; hence the injection did not end until sometime during the second period of measurement following administra-

14. Jahn, D.: Ueber die Beeinflussung des Energiestoffwechsels durch vegetative Reaktionen, *Deutsches Arch. f. klin. Med.* **166**:257-302, 1930.

15. Pijoan, M., and Gibson, J. G., II: The Rate of Disappearance of Intravenously Administered Dextrose in the Human Subject, *Am. J. Physiol.* **121**:534-536 (Feb.) 1938.

16. The observations on respiratory exchange were conducted by Basil James, with the assistance of George Lee in the gas analyses. The intravenous injections were made by Miss Dorothy V. Blanchard, R.N.

tion of the sugar. With 3 of the subjects 2 experiments with each method were made, and with 1 subject, 3 with each method. Samples of blood, from capillaries or from a vein, were taken in the postabsorptive period and one-half hour, one hour and two or two and one-half hours after the sugar was given.

### RESULTS

The results of the measurements of respiratory exchange (respiratory quotient and oxygen absorption) are shown graphically in figures 1 to 4. In P. D. S. the base line respiratory quotient before oral ingestion was in both cases lower than the base line respiratory quotient before intravenous injection. The respiratory quotient rose markedly after oral and also after intravenous administration. The oxygen absorption

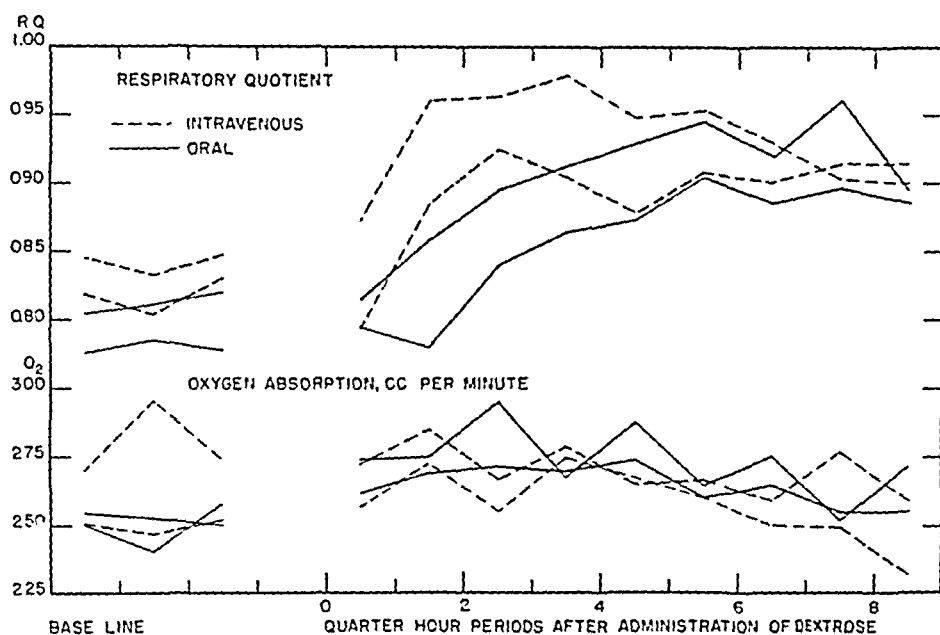


Fig. 1 (P. D. S.).—Respiratory exchange before and after oral and before and after intravenous administration of 50 Gm. of dextrose.

per minute was higher than the base line level for most of the two hours after oral ingestion. One of the base line oxygen values before intravenous injection was high and probably cannot be considered a true base line. If the other is accepted as correct, it would seem that the intravenous injection produced a rise in oxygen absorption in both series of experiments, which continued for at least two hours. Similarly in H. M. the respiratory quotients after the administration of sugar showed rises in both series of experiments and, for the most part, of about the same order of magnitude. The oxygen absorption after oral ingestion was raised, and after intravenous injection it was decidedly raised in 1 experiment but not in the other. In R. C. the respiratory quotient was raised after the administration of sugar in both series of experiments.

The oxygen absorption was higher after oral ingestion, but after intravenous injection there was, in 2 of the 3 experiments, little, if any, indication of a rise. In E. B. M. there was a marked rise both in the

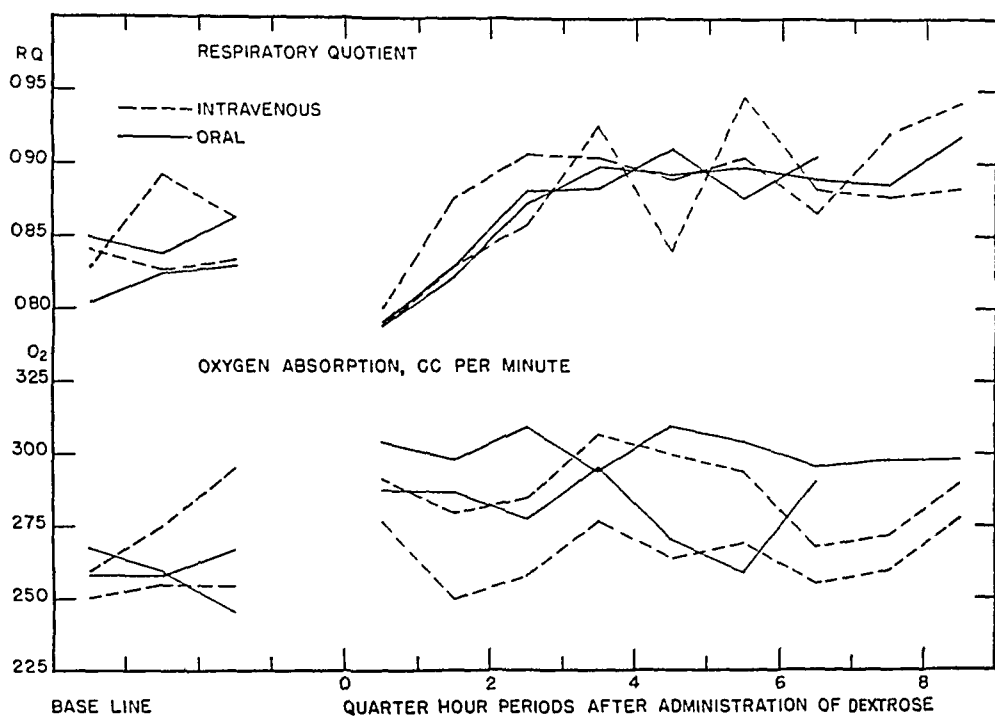


Fig. 2 (H. M.).—Respiratory exchange before and after oral and before and after intravenous administration of 50 Gm. of dextrose.

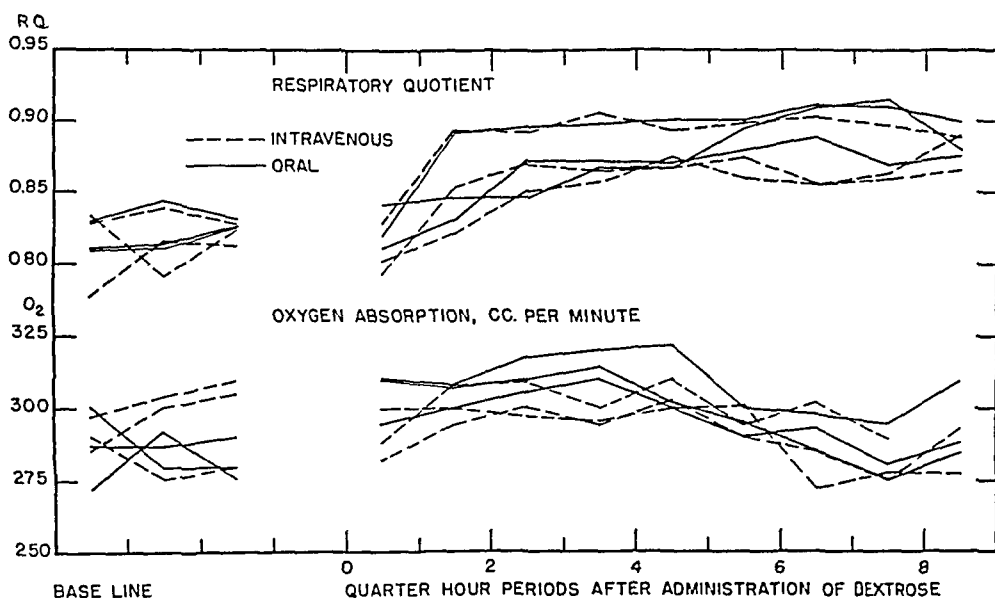


Fig. 3 (R. C.).—Respiratory exchange before and after oral and before and after intravenous administration of 50 Gm. of dextrose.

respiratory quotient and in oxygen absorption in both series of experiments. Considered graphically, the data do not show a marked difference between the changes either in the respiratory quotient or in oxygen



absorption after oral and after intravenous administration of 50 Gm. of dextrose.

Table 1 shows the effects of the method of administration of dextrose on the blood sugar and the urinary sugar. The base line values for

TABLE 1.—*Effect on the Sugar in the Blood and in the Urine of Normal Men of Oral and of Intravenous Administration of Fifty Grams of Dextrose*

Subject	Age, Yr.	Weight,* Kg.	Height, Cm.	Route of Adminis- tration	No. of Experi- ments	Sugar in Blood, %					Sugar in Urine, Gm.
						Base Line	After Dextrose				
							½ Hr.	1 Hr.	2 to 2½ Hr.		
P. D. S.	23	77.0	177	Oral.....	2	0.09	0.14	0.14	0.07	0.1	
				Intravenous	1	0.10	0.18	0.11	0.07	1.6	
H. M.	22	77.4	178	Oral.....	1	0.09	0.13	0.13	0.07	0.0	
				Intravenous	1	0.08	0.18	0.10	0.10	3.6	
R. C.	21	79.0	181	Oral.....	2	0.11	0.15	0.15	0.08	0.1	
				Intravenous	3	0.10	0.19	0.12	0.08	2.7	
E. B. M.	23	69.8	175	Oral.....	1	0.09	0.12	0.10	0.08	0.0	
				Intravenous	1	0.08	0.11	0.08	0.07	2.7	
Average.....				Oral.....	..	0.09	0.14	0.13	0.08	0.0	
				Intravenous	..	0.09	0.17	0.10	0.08	2.7	

\* Without clothes.

TABLE 2.—*Increases in Heat Production and in Carbohydrate Combustion in Normal Men During Two and One-Quarter Hours After Oral and After Intravenous Administration of Fifty Grams of Dextrose*

Subject	Route of Administration	No. of Experiments	Heat Production, Calories				Carbohydrate Combustion, Gm.			
			Increase Above Base Line				Increase Above Base Line			
			Base Line	Range	Average	Difference	Base Line	Range	Average	Difference
P. D. S.	Oral.....	2	160.4	13.1-18.4	15.7		9.1	11.8-15.0	13.4	
	Intravenous	2	160.0	8.4-18.7	13.6	— 2.1	13.2	11.1-15.8	13.4	±0.0
H. M.	Oral.....	2	167.7	17.7-27.5	22.6		15.2	7.1- 9.0	8.0	
	Intravenous	2	171.3	8.6- 9.7	9.2	—13.4	17.0	5.5- 6.2	5.9	—2.1
R. C.	Oral.....	3	183.7	8.0-17.1	13.3		15.2	9.1-10.5	9.9	
	Intravenous	3	182.1	6.8-14.4	9.8	— 3.5	14.1	6.9- 9.8	8.4	—1.5
E. B. M.	Oral.....	2	161.3	15.1-19.5	17.3		17.4	9.7-12.3	11.0	
	Intravenous	2	161.3	16.2-16.7	16.4	— 0.9	16.1	7.7- 8.7	8.2	—2.8
Average	Oral.....	..	.....	.....	17.2		.....	.....	10.6	
	Intravenous	..	.....	.....	12.3	— 5.0	.....	.....	9.0	—1.6

blood sugar lie within a narrow range and are normal. One-half hour after administration of sugar the blood sugar was in all subjects with the exception of E. B. M. higher after intravenous injection than after oral ingestion and above the threshold for escape of urinary sugar. At one hour after intravenous injection, on the contrary, the blood sugar was in all cases lower than one hour after oral ingestion. There was no significant difference in the values at two to two and a half hours. In

all the observations with intravenous injection there was an elimination of sugar in the urine, varying from 1.6 Gm. in P. D. S. to 3.6 Gm. in H. M. After oral ingestion there was a trace of sugar in the urine in 2 subjects.

The increases in heat production after the administration of sugar are summarized in table 2. The ranges in the increases are wide for most of the groups of experiments, but on the whole the oral ingestion resulted in a greater increase in heat production than the intravenous injection. This was most marked in H. M. and least marked in E. B. M.

The increases in carbohydrate combustion are also summarized in table 2. In P. D. S. the method of administration of sugar made no

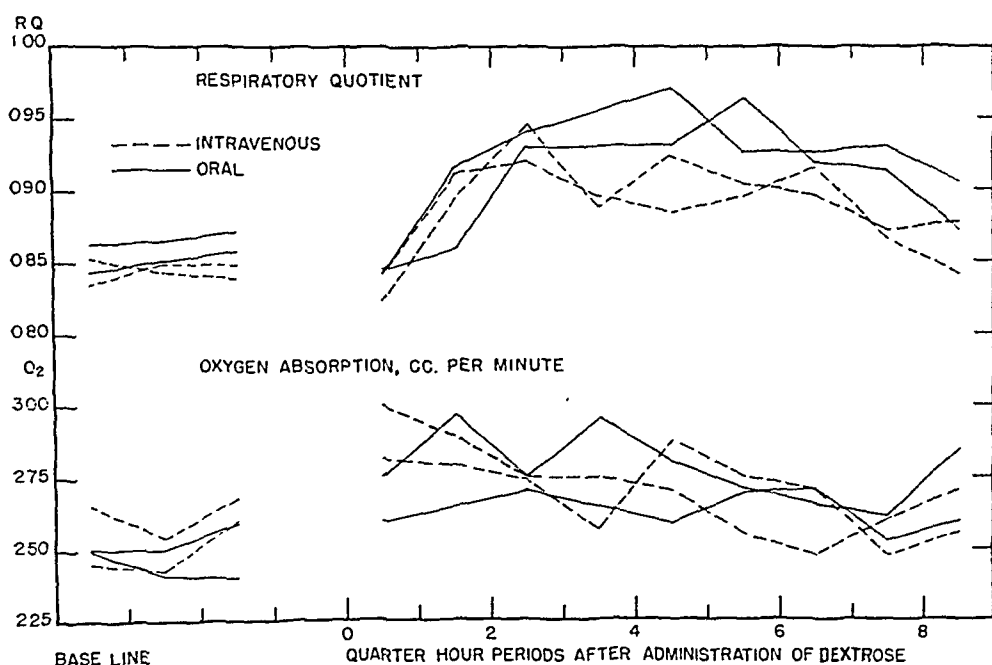


Fig. 4 (E. B. M.).—Respiratory exchange before and after oral and before and after intravenous administration of 50 Gm. of dextrose.

difference, on the average, in the increase in carbohydrate combustion. The other 3 subjects showed a slightly lower carbohydrate combustion after intravenous injection than after oral ingestion, the differences ranging from 1.5 to 2.8 Gm. In the main, these correspond closely to the differences between the elimination of sugar in the urine in the comparison of oral and of intravenous administration shown in table 1. The observations lasted only two and one-quarter hours after the administration of the sugar, and it is probable that this period was not long enough to include all the increases in carbohydrate combustion. Therefore, this good comparison between differences in carbohydrate combustion and in elimination of sugar in the urine may be more apparent than real.

The results indicate that in these normal men for two and one-quarter hours after the administration of 50 Gm. of dextrose the rises in respiratory quotient were practically the same whether the sugar was given by mouth or by vein, and consequently there was little difference in the carbohydrate combustion. The oral ingestion gave an insignificantly higher carbohydrate combustion and a greater increase in heat production than did the intravenous injection, whereas the latter method of administration resulted in a more definite elimination of sugar in the urine, there being practically no such elimination after oral ingestion.

#### SUMMARY

In 4 normal men the blood sugar was higher one-half hour after and lower one hour after intravenous injection of 50 Gm. of dextrose than it was at the same times after oral ingestion of the same amount, but there was no difference in the values after two to two and one-half hours. Sugar was eliminated in the urine only after intravenous injection. The increases in respiratory quotient, heat production and carbohydrate combustion above the postabsorptive base lines were insignificantly greater after oral than after intravenous administration.

# BLOOD PYRUVIC ACID IN HEART DISEASE

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CHICAGO

Meakins and Long<sup>1</sup> were the first to study intermediates of tissue carbohydrate metabolism in heart disease. In 1927 they showed a marked and proportional increase in blood lactic acid in patients with heart failure. The validity of these results was subsequently both confirmed<sup>2</sup> and denied.<sup>3</sup> The importance of lactic acid as the center of carbohydrate metabolism has since been overshadowed by that of pyruvic acid, and recently even more interest has attached itself to pyruvic acid because of Peters'<sup>4</sup> discovery that the presence of vitamin B<sub>1</sub> is necessary for its oxidation.

In 1937 Taylor, Weiss and Wilkins<sup>5</sup> attempted estimations of blood pyruvic acid on persons with all types of disease by measuring the blood bisulfite-binding substances and showed a rise of these in subjects with failing hearts. This method of pyruvate estimation has since been shown, however, to be nonspecific and inaccurate.<sup>6</sup> This present work makes use of the specific method of Lu<sup>7</sup> and deals only with heart disease.

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From the Lasker Foundation for Medical Research and the Department of Medicine of the University of Chicago.

✓ 1. Meakins, J., and Long, C. N. H.: Oxygen Consumption, Oxygen Debt, and Lactic Acid in Circulatory Failure, *J. Clin. Investigation* **4**:273 (June) 1927.

✶ 2. Harris, I.; Jones, E. W., and Aldred, C. N.: Blood  $p_H$  and Lactic Acid in Different Types of Heart Disease, *Quart. J. Med.* **4**:407 (Oct.) 1935.

✓ 3. Weiss, S., and Ellis, L. B.: Oxygen Utilization and Lactic Acid Production in the Extremities During Rest and Exercise in Subjects with Normal and in Those with Diseased Cardio-Vascular Systems, *Arch. Int. Med.* **55**:665 (April) 1935.

4. Peters, R. A.: Biochemical Lesion in Vitamin B<sub>1</sub> Deficiency—Application of Modern Biochemical Analysis and Its Diagnosis, *Lancet* **1**:1161 (May 23) 1936.

5. Taylor, F. H. L.; Weiss, S., and Wilkins, R. W.: The Bisulfite Binding Power of the Blood in Health and in Disease, with Special Reference to Vitamin B<sub>1</sub> Deficiency, *J. Clin. Investigation* **16**:833 (Nov.) 1937.

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7. Lu, G. D.: Studies on the Metabolism of Pyruvic Acid in Normal and Vitamin B<sub>1</sub> Deficient States: I. A Rapid Specific and Sensitive Method for the Estimation of Blood Pyruvate, *Biochem. J.* **33**:249 (Feb.) 1939.

## METHOD

The levels of pyruvate in the blood of organically normal subjects and patients with decompensated and with compensated heart disease were studied. The control group consisted of 5 male and 5 female subjects with psychopathic disorders, all carefully selected, ranging in age from 25 to 84; none of them was addicted to alcohol, had any evidence of organic disease or dietary deficiency or was excited or depressed. A pyruvate determination was done on each subject daily for six days and after one-half hour of rest in bed. Twenty hospital patients aged 32 to 79 with varying degrees of congestive failure and with no fever, history of dietary deficiency or impaired renal function other than that due to the cardiac failure and no other organic disease constituted the second group on whom daily determinations of blood pyruvate were made. In the third group were 12 patients aged 20 to 62 with heart disease but without failure; single determinations were done on these patients.

## RESULTS AND COMMENT

The values for blood pyruvic acid obtained in 60 determinations on the physically normal group (table 1) varied between 0.56 and 1.1 mg.

TABLE 1.—*Range and Mean Levels of Pyruvate in the Blood of Controls*

Subject No.	Blood Pyruvate, Mg./100 Cc.	
	Range*	Mean
24.....	0.5-0.8	0.68
25.....	0.7-0.8	0.76
26.....	0.8-1.0	0.92
27.....	0.8-1.0	0.92
28.....	0.8-1.0	0.88
29.....	0.6-0.9	0.76
30.....	0.6-0.9	0.79
31.....	0.6-1.1	0.88
33.....	0.6-0.9	0.73
34.....	0.6-1.0	0.80

\* The range is based on six daily determinations.

per hundred cubic centimeters, with a mean of 0.8 mg. Only one value was above 1.0 mg.

The maximum blood pyruvate was significantly elevated in all of the patients with decompensated heart disease except 1 (table 2). The mean "peak" rise for the group was 2.15, with a range of 1.2 to 3.4 mg. per hundred cubic centimeters.<sup>8</sup>

The blood pyruvate curve of each patient in failure was generally in accord with his clinical course (table 3). The 4 patients who left the hospital with hearts compensated (5, 15, 17 and 20) had normal values at the end of their stay in the hospital. Three patients (6, 12 and 18) were discharged with hearts still slightly decompensated. Their terminal levels of blood pyruvate were at the upper limits of normal. Two patients

8. This roughly approximates the values that Platt and Lu (Chemical and Clinical Findings in Beriberi with Special Reference to Vitamin B<sub>1</sub> Deficiency, Quart. J. Med. 29:355 [July] 1936) obtained on subjects with acute beriberi.

who left the hospital with hearts decompensated (1 and 8) had continuously high levels of pyruvate during their entire hospital stay. The 2 patients (4 and 19) who remained refractory to treatment during this study also showed constantly elevated levels of pyruvate.

Every patient but 1 showed changes from day to day. These variations, however, were not considered significant unless they were higher than 0.3 mg. per hundred cubic centimeters, the maximum day to day variation of the controls. An attempt was made to correlate the daily fluctuation with the clinical condition on the same day. If one allows for one discordant variation, 80 per cent of the patients showed daily

TABLE 2.—*Highest Level of Pyruvate (Peak) in the Blood of Patients with Decompensated Heart Disease*

Subject No.	Type of Heart Disease*	Severity of Condition*	Peak, Mg./100 Cc.
1.....	H	S	3.4
2.....	H	S	1.9
3.....	A	S	2.0
4.....	A	M	2.2
5.....	A	M	1.8
6.....	A	M	2.0
7.....	A	S	2.3
8.....	H	M	1.8
10.....	A	S	1.9
11.....	H	S	2.2
14.....	A	S	2.1
15.....	R	M	1.4
17.....	R	M	1.2
18.....	U	M	1.7
19.....	H	S	2.5
20.....	R	M	1.5
21.....	H	S	1.7
22.....	CT	S	1.7
47.....	A	M	1.5
49.....	R	S	1.8

\* The following abbreviations have been employed: H, hypertension; A, arteriosclerosis; R, rheumatic heart disease; CT, coronary thrombosis; U, unknown; S, severe, and M, moderate.

variations in agreement with the corresponding clinical changes. Or of a sum total of fifty-eight daily variations in all of the patients, 43, or 74 per cent, were clinically correlative.

It should be remembered, however, that clinical estimation of the day to day change of the condition of a patient with heart disease is difficult, if not at times impossible. It is quite possible, therefore, that even though a given daily level of pyruvate does not fit in with the clinical evaluation of that day the former may still be the better criterion of the patient's true condition. That the mean peak of pyruvate in the blood of patients with severe failure was 2.13 mg. per hundred cubic centimeters as contrasted with 1.67 mg. for those moderately ill may be further evidence in this direction.

Of the 7 patients who died, 3 showed a rise of blood pyruvate as death approached, 3 no change and 1 a fall. It is interesting to note

TABLE 3.—Daily Levels of Pyruvate in the Blood of Patients with  
Decompensated Heart Disease

Subject No.*	Blood Pyruvate, Mg./100 Cc., and Clinical Condition †												Comment	
1.....	2.3	1.9	3.4	2.1	1.8	1.5	1.2	1.4	1.5	1.7‡				Left hospital with heart de- compensated
		I	S	I	I	S	S	S	S	W				
2.....	1.9	1.3	1.6	1.5										Critically ill on entrance
		I	W	S	Died									
3.....	1.4	1.4	1.8	0.9	0.8	1.4	0.9	1.0	1.3	1.5	2.0	Died		Progressed satisfactorily for 8 days; became semicomatose on 9th day
		S	S	S	I	S	I	S	W	W	W			
4.....	0.9	2.2	1.6	1.1	0.9	1.4	0.9	1.7	1.5	1.5	1.2	2.0	1.5	Refractory to treatment; re- mained in hospital
		I	I	W	S	W	S	S	S	S	W	I	S	
5.....	1.8	1.3	1.5	0.9	0.7	0.5	0.9	0.7	0.7	1.2	0.6	0.7		Discharged with heart compen- sated
		I	I	I	I	I	S	S	S	S	S	S		
6.....	1.8	1.9	2.0	1.0	1.5	1.2	1.2	0.9	1.0	1.5‡				Discharged with slight decompensation
		S	S	I	S	I	I	I	W	W				
7.....	1.4	2.0	2.3											Suddenly became critically ill on 3rd day
		W	W	Died										
8.....	1.7	1.7	1.8	1.2	1.4	0.8	1.3	0.9	1.4	1.5	1.8	1.7		Heart never compensated; discharged
		I	I	I	S	I	W	I	W	S	W	S		
10.....	0.8	0.8	1.5	1.9	1.5	1.4								Severely ill on entrance; be- came critically ill on 3rd day
		I	W	S	W	W	Died							
12.....	2.2	1.8	1.6	1.6	1.2	1.5	1.7	1.0	1.0	1.4‡				Discharged with slight decompensation
		I	S	I	I	S	S	W	S	W				
14.....	2.1	1.4	1.5	1.5	1.9									Severely ill on entrance
		W	S	S	W	Died								
15.....	1.4	1.4	1.2	1.3	0.7	1.4	0.9	0.9						Discharged with heart compensated
		S	I	I	I	W	I	S						
17.....	1.0	1.2	1.1	0.8	0.7	0.9								Discharged with heart compensated
		S	I	I	I	I								
18.....	1.4	1.2	1.1	1.7	1.7	5.0§	0.9	1.5	1.1					Heart almost compensated on last day
		S	I	W	S	W	I	S	I					
19.....	1.8	1.5	1.6	1.6	1.5	1.5	1.7	1.6	1.6	2.5				Remained refractory to treat- ment; died later
		S	S	S	S	S	S	S	S	W				
20.....	1.5	1.2	1.4	1.0	1.5	1.2	1.1	1.0	0.8	0.8				Discharged with heart compensated
		I	S	I	W	I	I	I	I	I				
21.....	1.7	1.5												Entered critically ill
		W	Died											
22.....	1.7	1.5												Entered critically ill
		W	Died											

\* For the type of heart disease see table 2.

† The following abbreviations have been employed: I, improved; S, same, and W, worse.

‡ This value for blood pyruvate was obtained at home after the patient left the hospital.  
In all cases the patients were definitely clinically worse at home.

§ Patient got out of bed without permission.

TABLE 4.—Level of Pyruvate in the Blood of Patients with Compensated  
Heart Disease

Subject No.	Type of Heart Disease*	Blood Pyruvate, Mg./100 Cc.
35.....	R	0.8
36.....	R	0.6
37.....	A	0.8
38.....	A	0.6
39.....	A	0.7
41.....	R	0.8
43.....	H	0.9
44.....	H	0.8
53.....	H	0.6
54.....	H	0.7
55.....	H	1.1
56.....	A	0.8

\* The following abbreviations have been employed: R, rheumatic; A, arteriosclerotic, and H, hypertensive.

that in 2 patients with edema of noncardiac origin which were also studied the blood pyruvate showed no rise above the normal level at any time.

Patients 4, 8 and 10 had "high normal" values on two occasions each, even though their hearts remained constantly decompensated. In patient 4 this occurred only twice in a total of thirteen determinations; in patient 12, twice in a total of twelve determinations, and in patient 10, twice in a total of six determinations. I have no explanation for these few divergent values.

Two patients with heart disease and with serous effusions were studied (patients 47 and 49, table 2). The blood of 1 contained 1.5 mg. of pyruvate per hundred cubic centimeters at a time when the pleural fluid contained 1.4 mg. per hundred cubic centimeters. The blood pyruvate of the second patient was 1.6 mg. per hundred cubic centimeters, with the pyruvate concentration of the ascitic fluid 2.7 mg. per hundred cubic centimeters.

For the group with compensated hearts (table 4) 12 patients with definite cardiac enlargement (10 to 110 per cent oversized) were selected for study. It is significant that the pyruvate levels were well within normal limits. Of further interest were 2 ambulatory patients with heart disease in whom compensation appeared to be complete except for a definite but slight edema, and they both had increased values of 1.2 mg. of pyruvate per hundred cubic centimeters of blood.

The answer to the question of why blood pyruvic acid increases in persons with heart failure can only be one of speculation. Increased utilization of dextrose and its intermediates may occur and might explain the accumulation of pyruvic acid in the blood. A second possibility is that the anoxia of the failing circulation may prevent the oxidation of pyruvic acid and hence contribute to its accumulation. Circulatory sluggishness or mechanical impediment to the removal of the excess pyruvic acid from the blood may also play a role.

It is conceivable that serial estimations of the pyruvic acid in the blood of patients with heart disease might prove valuable in following the course of the disorder.

#### CONCLUSIONS

1. There is a rise above normal of pyruvic acid in the blood of persons with heart failure.
2. This elevation approximates the degree of failure.

Dr. Emmet B. Bay contributed helpful suggestions and criticisms, and Dr. E. S. G. Barron permitted me the use of his laboratory and gave technical guidance.

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# EFFECT OF UNDERNUTRITION ON CARDIAC OUTPUT AND CARDIAC WORK IN OVERWEIGHT SUBJECTS

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The purpose of this study is to demonstrate the beneficial effect of undernutrition and reduction in weight on the heart and circulation. The influence of a low calory diet on pulse rate, blood pressure, oxygen consumption, arteriovenous oxygen difference and cardiac output was determined over a long period in normal overweight subjects.

In obesity the heart functions under two handicaps. In the first place, the increased surface area results in an absolute rise in total body metabolism and oxygen consumption, which augments the work of the heart. Secondly, the elevated diaphragm limits the respiratory movements and compresses the lungs, causing a reduction in vital capacity. Both of these factors place a burden on the heart and explain the tendency of obese persons to fatigue and to dyspnea on mild effort, indicative of diminished exercise tolerance.

In studies on dietary restriction in subjects of normal weight Benedict and his co-workers<sup>1</sup> observed a drop in oxygen consumption, basal metabolic rate, pulse rate and blood pressure. Master and his co-workers<sup>2</sup> demonstrated similar changes in patients with acute and

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1. Benedict, F. B.; Miles, W. R.; Roth, P., and Smith, H. M.: *Human Vitality and Efficiency Under Prolonged Restricted Diet*, Publication 280, Carnegie Institution of Washington, 1919.

2. Master, A. M.; Jaffe, H. L., and Dack, S.: *Undernutrition in the Treatment of Coronary Artery Disease (Particularly Thrombosis): Effect on the Basal Metabolism and Circulation*, *J. Clin. Investigation* **15**:353, 1936; *A Study of One Hundred and Fifty Cases of Coronary Thrombosis Treated with Low Calory Diet*, *Am. Heart J.* **10**:1102, 1935.

with chronic coronary artery disease and emphasized the beneficial effects of undernutrition in these conditions as well as in heart failure. In addition to the aforementioned effects on the circulation, Proger and Magendantz<sup>3</sup> observed also a decrease in cardiac output in patients with congestive heart failure on prolonged dietary restriction. Roemheld,<sup>4</sup> investigating the effect of restriction of fluids and salt as well as caloric intake on normal subjects and on patients with cardiac disease, found that after three to five days the cardiac output showed an average drop of 0.25 liter per minute. However, the results pertaining to the low calory diet (980 calories daily for three days) were inconclusive, since the changes were within physiologic limits of variation and since the period of observation was too short.

#### MATERIAL AND METHOD

Our observations were made on 5 overweight subjects whose ages ranged from 15 to 50 years and whose actual weight exceeded the ideal weight by 19 to 30 per cent. They were placed on a 1,200 calory diet; they remained ambulatory and continued to perform their usual activities. We made cardiac output determinations once or twice weekly for several months, using the three sample modification of the Grollman acetylene method.<sup>5</sup> All the determinations were made before breakfast with the subjects in the basal state, in the semirecumbent position. We checked our results by the Wetzler-Boeger method<sup>6</sup> based on physical principles; the cardiac output is calculated by determining the pulse wave velocity, the pulse pressure and the diameter of the aorta. Results of comparative determinations employing both methods checked within 10 per cent. The cardiac work was computed in kilogram-meters per minute, according to the formula

$$\text{work} = Q \times R + \frac{MV^2}{2}.^7$$

#### RESULTS

The results are summarized in the table. It will be seen that the average loss of weight was 12 per cent of the initial weight. This was

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3. Proger, S. H., and Magendantz, H.: Effect of Prolonged Dietary Restriction on Patients with Cardiac Failure, *Arch. Int. Med.* **58**:703 (Oct.) 1936.

4. Roemheld, L.: Beeinflussung des Herzminutenvolumens durch Diät, *Ztschr. f. Kreislaufforsch.* **31**:73-82, 1939; Untersuchungen ueber den Einfluss kalorienarmer Ernährung auf das Herzminutenvolumen des Menschen, *ibid.* **31**:668-671, 1939.

5. Grollman, A.: *The Cardiac Output of Man in Health and Disease*, Springfield, Ill., Charles C. Thomas, Publisher, 1932.

6. Wetzler, K., and Boeger, L.: *Die Dynamik des arteriellen Systems*, *Ergebn. d. Physiol.* **41**:1, 1939.

7.  $Q$  = cardiac output;  $R$  = peripheral resistance as measured by the mean arterial pressure;  $M$  = mass of stroke output;  $V$  = blood velocity. The factor  $\frac{MV^2}{2}$  is normally 0.7 gram-meter per stroke and as a rule is negligible (Wiggers, C. J.: *Physiology in Health and Disease*, Philadelphia, Lea & Febiger, 1939). We have therefore omitted it in our calculations.

accompanied by an average drop of 13 per cent in oxygen consumption, an average rise of 26 per cent in the arteriovenous oxygen difference and an average decrease of 30 per cent in cardiac output and of 35 per cent in cardiac work. The basal metabolic rate did not change appreciably. There was an average decrease of 10 beats per minute in the pulse rate and of 11 mm. in the systolic blood pressure. Short résumés of the 5 cases are presented.

#### REPORT OF FIVE CASES

CASE 1.—A. D., a man aged 26, was 70 inches (178 cm.) tall and in perfect health (fig. 1). His initial weight of 202 pounds (92 Kg.) was 30 per cent greater than his ideal weight. The blood pressure was 120 systolic and 75 diastolic; the basal pulse rate, 68 per minute, and the oxygen consumption, 254 cc. per minute. The cardiac output measured 4.8 liters per minute. After being on a 1,200 calory diet for eleven weeks, he lost 32 pounds (15 Kg.), equivalent to 16 per cent of his initial weight. During that time, the blood pressure dropped to 100 systolic and 60 diastolic, and the pulse rate, to 56 per minute. The oxygen consumption fell to 200 cc. per minute, a drop of 20 per cent, and the arteriovenous oxygen difference increased 32 per cent. Simultaneously, the cardiac output dropped to 2.75 liters per minute, and the cardiac work was decreased from 5.9 to 3.0 kilogram-meters per minute. An appreciable change in oxygen consumption and cardiac output did not occur until the fifth to the sixth week, after the patient had lost approximately 20 pounds (9 Kg.). After seventy-seven days the caloric intake was increased to 1,500; the weight was maintained, and the oxygen consumption, cardiac output and cardiac work increased slightly but remained below the initial levels.

CASE 2.—M. U., a 40 year old housewife, was 71 inches (180 cm.) tall and weighed 230 pounds (104 Kg.), that is, 27 per cent more than her ideal weight (fig. 2). The blood pressure was 115 systolic and 75 diastolic and the pulse rate, 70 per minute. The initial cardiac output measured 3.75 liters per minute, and the cardiac work, 5.1 kilogram-meters per minute. During a period of approximately seven months on a low calory diet the subject lost 35 pounds (16 Kg.), that is, 15 per cent of the initial weight. This loss was accompanied by a drop in oxygen consumption from 249 to 210 cc. per minute, representing a decrease of 16 per cent. The arteriovenous oxygen difference increased 23 per cent, and the cardiac output fell to 2.8 liters per minute, and the cardiac work, to 3.1 kilogram-meters per minute. The blood pressure dropped to 95 systolic and 68 diastolic, and the pulse rate, to 60 per minute. As in case 1, an appreciable effect was not noted until the eighth week, after the subject had lost 12 pounds (5 Kg.) in weight.

CASE 3.—E. B., a 15 year old boy, was 66 inches (167 cm.) tall and weighed 176 pounds (80 Kg.), which was 21 per cent above the ideal weight (fig. 3). On a 1,200 calory diet he lost only 6 pounds (3 Kg.) in three months. It was found that despite this slight loss of weight the arteriovenous oxygen difference rose 40 per cent, the cardiac output fell from 4.6 to 3.3 liters per minute and the cardiac work decreased from 5.1 to 4.1 kilogram-meters per minute. This apparent discrepancy was explained by the fact that the subject's height had increased 3 inches (7 cm.). Growth is normally accompanied by an increase in oxygen consumption, but the latter remained approximately the same in this growing boy while he was on a low calory diet. Therefore, there was actually

TABLE 1.—*Effects of Undernutrition on the Heart and the Circulation in Overweight Subjects*

Subject	Sex	Age, Yr.	Height, In.	Weight, Lb.		Pulse Rate per Min.	Blood Pressure, Mm. Hg	Vital Capacity, Cc.	Basal Metabolic Rate, %	Oxygen Consump- tion, Cc./Min.	Arterio- venous Oxygen Difference, Cc./L.	Cardiac Output, L./Min.	Cardiac Work, Kg.-M./Min.
				Actual	Ideal								
A. D.	♂	26	70	202	155	68	120/75	3,000	-15	251	53	4.8	5.9
			170		56	100/60	3,500	-15	200	70	2.75	3.1	
M. U.	♀	40	71	230	180	70	115/75	2,600	-8	249	65	3.75	5.1
			195		60	95/68	2,900	-9	210	80	2.8	3.1	
E. B.	♂	15	66	176	145	76	100/60	3,200	-8	262	57	4.6	5.1
			69	170		70	105/65	3,500	-8	265	80	3.3	4.1
M. H.	♀	18	67	172	146	70	110/70	2,800	-16	225	65	3.5	4.5
				152		60	105/70	3,100	-13	192	79	2.5	2.9
J. F.	♀	50	61	179	150	68	120/80	2,900	-12	220	69	3.1	4.3
				157		58	105/70	3,200	-10	184	78	2.3	2.9
Summary of Changes													
Range.....				-3 to -16%		-6 to -12	+5 to -20	+9 to +17%	+3 to -1%	+1 to -20%	+13 to +40%	-26 to -43%	-20 to -49%
Average.....				-12%		-10	-11	+12%	+1%	-13%	+26%	-30%	-35%

a relative decrease in oxygen consumption, and the loss in weight of 6 pounds is significant. The pulse rate and the blood pressure did not show any definite change.

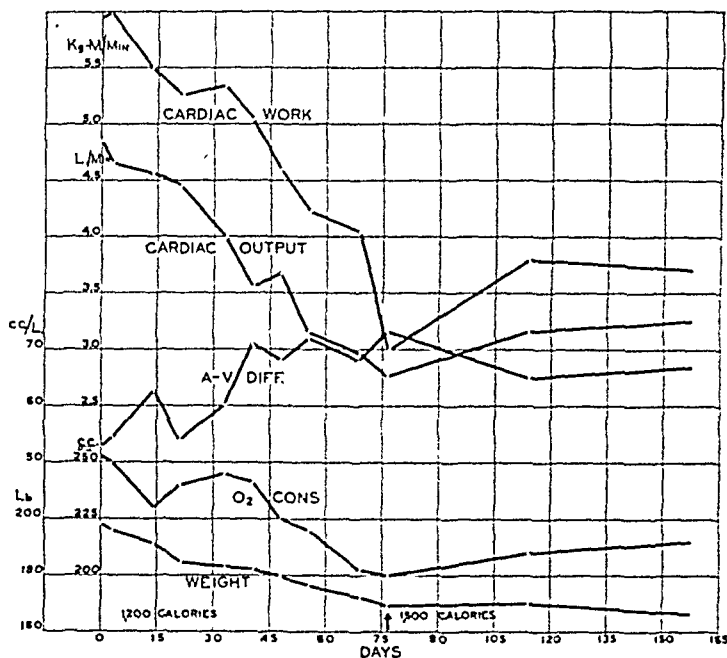


Fig. 1 (case 1).—A. D., a 26 year old man, 5 feet 10 inches (178 cm.) tall.

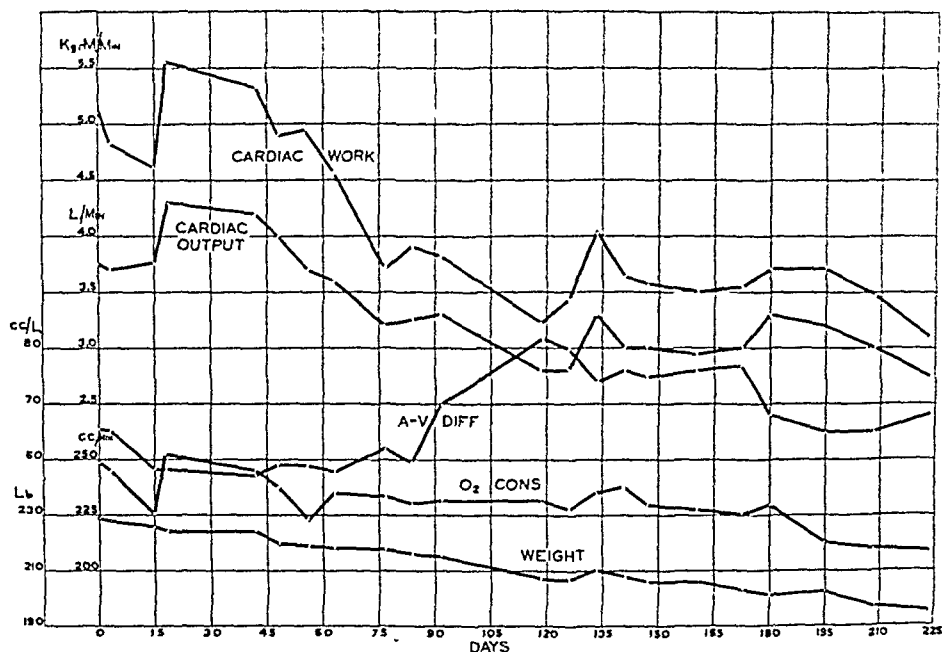


Fig. 2 (case 2).—M. U., a 40 year old woman, 5 feet 11 inches (180 cm.) tall.

CASE 4.—M. H., a woman aged 18, was 67 inches (170 cm.) tall and weighed 172 pounds (78 Kg.), 19 per cent above the ideal weight (fig. 4). After almost three months on a 1,200 calorie diet she lost 20 pounds (9 Kg.). The oxygen

consumption fell from 225 to 192 cc. per minute, a drop of 15 per cent; the arteriovenous oxygen difference rose 22 per cent, and the cardiac output dropped from 3.5 to 2.5 liters per minute, a decrease of 28 per cent. The blood pressure

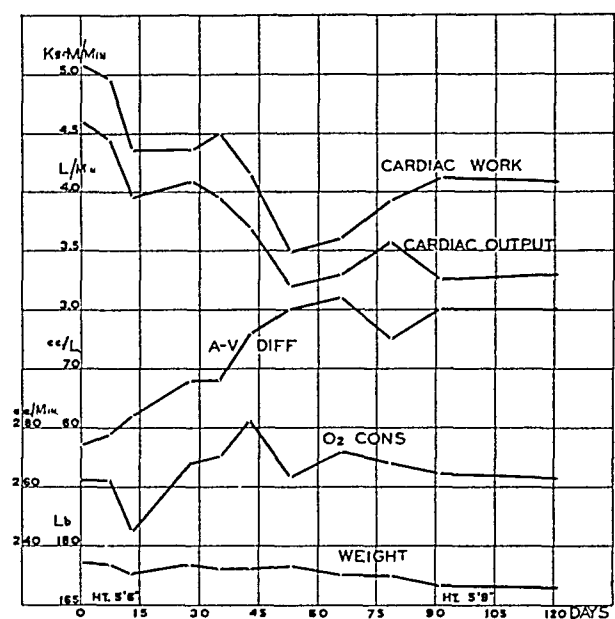


Fig. 3 (case 3).—E. B., a 15 year old boy, 5 feet 6 inches to 5 feet 9 inches (167 to 174 cm.) tall.

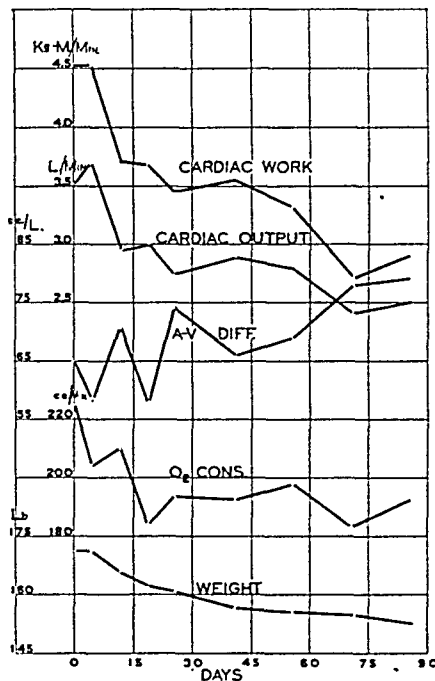


Fig. 4 (case 4).—M. H., an 18 year old woman, 5 feet 7 inches (170 cm.) tall.

did not change, but the pulse rate fell from 70 to 60 per minute. The cardiac work was diminished from 4.5 to 2.9 kilogram-meters per minute (36 per cent). Since the loss of weight was rapid during the first two weeks, distinct changes in circulatory dynamics were noted as early as the third week.

CASE 5.—J. F., a woman aged 50, was 64 inches (162 cm.) tall and weighed 179 pounds (81 Kg.), 20 per cent above the ideal weight (fig. 5). On a 1,200 calory diet she lost 22 pounds (10 Kg.) in approximately two months. During this period the oxygen consumption fell from 220 to 184 cc. per minute, a drop of 16 per cent, and the arteriovenous oxygen difference increased 13 per cent. The cardiac output dropped from 3.1 to 2.3 liters per minute and the cardiac work was reduced from 4.3 to 2.9 kilogram-meters per minute. The blood pressure dropped from 120 to 105 systolic and from 80 to 70 diastolic, and the pulse rate, from 68 to 58 per minute. The earliest effects were noted two weeks after institution of the low calory diet.

*Comment.*—Cardiac output was also measured in 3 cases in which the subjects did not lose any weight as a result of nonobservance of the diet or of endogenous factors. The cardiac output and other circulatory

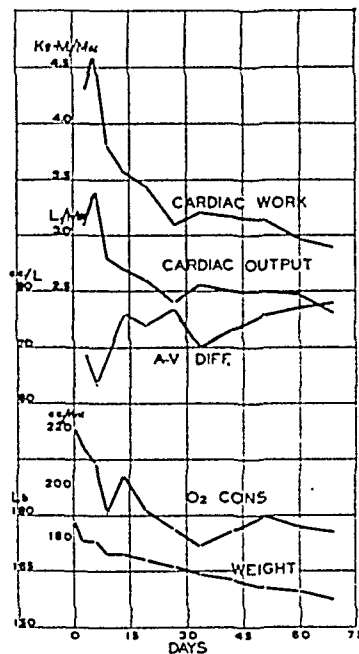


Fig. 5 (case 5).—J. F., a 50 year old woman, 5 feet 4 inches (157 cm.) tall.

factors did not change except for slight physiologic variations that occur from day to day.

#### COMMENT

It has been shown that undernutrition and reduction in weight in normal obese subjects slows the basal pulse rate and reduces the oxygen consumption, the cardiac output and the work of the heart. The reduction in cardiac output is determined chiefly by two factors: a fall in oxygen consumption, produced by the decrease in surface area occurring in undernutrition, and a rise in arteriovenous oxygen difference, the so-called coefficient of oxygen utilization. The increased arteriovenous oxygen difference is a manifestation of improved oxygen utilization and accounts for the fact that the decrease in cardiac output is proportionally

greater than that in oxygen consumption. The cardiac work is reduced, since it is proportional to cardiac output and peripheral resistance, as measured by mean arterial pressure. The reduction in the work of the heart was actually 33 to 49 per cent in 4 of the 5 cases reported. The pulse rate and the pulse pressure decreased with weight reduction. The drop in pulse rate, a vagal effect brought about by the lowered metabolic rate, increases the efficiency of the heart, since diastole is prolonged.

In previous studies in undernutrition by Benedict<sup>1</sup> and Master<sup>2</sup> and their associates a distinct lowering of the basal metabolic rate as well as of the oxygen consumption was observed. Only a minority of subjects in these two series were overweight. In our overweight subjects there was no definite effect on the basal metabolic rate despite the diminution in total body metabolism.

Another advantageous change noted in our subjects was an increase of 10 to 17 per cent in vital capacity. As stated previously, obesity is associated with elevation of the diaphragm, which limits the respiratory movements and places a great burden on the pulmonary circulation. Loss of weight is accompanied by a lowering of the diaphragm, facilitating expansion of the lungs and increasing vital capacity. The latter results in improved exercise tolerance and diminution of dyspnea on effort.

An important application of the circulatory effects of undernutrition lies in the treatment of patients with cardiac disease, particularly those who are overweight, in whom dietary restriction causes an increase in cardiac reserve, combats the tendency to heart failure and prevents attacks of angina pectoris on effort by decreasing the basal work of the heart. Effort results in increased muscular action, which in turn augments the requirements for oxygen, cardiac output and coronary circulation. Since there is a disproportion between oxygen requirement and supply in the presence of coronary artery disease, angina pectoris due to coronary insufficiency occurs. Under such circumstances reduction in weight acts beneficially by lowering the basal cardiac output and raising the threshold for anginal attacks. For example, if the basal cardiac work is 5.9 kilogram-meters per minute (case 1), the limit of coronary supply is reached quickly during effort. After reduction in weight the basal cardiac work is lowered, in this case to 3.0 kilogram-meters per minute, allowing for greater increase in coronary circulation and thus raising the threshold for an anginal attack by 2.9 kilogram-meters per minute. This is the chief benefit of undernutrition to patients with coronary artery disease. Restriction of the diet of patients with such disease, particularly if they are overweight, is of the utmost importance in the prevention of attacks of angina pectoris.



## SUMMARY

The effect of reduction in weight on the oxygen consumption, pulse rate, blood pressure, cardiac output and cardiac work was studied in 5 normal overweight subjects who were placed on a 1,200 calory diet. The modified Grollman acetylene method and the Wetzler-Boeger physical method were used to determine the cardiac output. Loss of weight was accompanied by an average drop of 16 per cent in oxygen consumption, an average increase of 24 per cent in the arteriovenous oxygen difference and an average drop of 30 per cent in the cardiac output. These changes were accompanied by slowing of the pulse rate and slight lowering of the blood pressure. Since cardiac work is a function of cardiac output and mean arterial pressure, it was calculated that the low caloric intake and the reduction in weight resulted in a distinct diminution in the work of the heart (average, 35 per cent). This is of great benefit to overweight persons, in whom the cardiac work is increased, and is of particular importance in the treatment of patients with heart disease, whose cardiac reserve is diminished and who are barely able to compensate for any additional strain.

# PERSISTENCE AND RECURRENCE OF TOXIC GOITER FOLLOWING SUBTOTAL THYROIDECTOMY

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While subtotal thyroidectomy is a successful procedure in most patients with toxic goiter, it is followed in some instances by the persistence or recurrence of signs and symptoms of the disease. In a previous study one of us (W. O. T.) and associates<sup>1</sup> reported observations on patients with postoperative thyrotoxicosis seen at the Massachusetts General Hospital, Boston. The present study was undertaken to compare the disease in an area in which simple goiter is prevalent (Chicago) with that in an area in which simple goiter is rare (Boston) and to secure further information concerning the cause, duration and types of postoperative thyrotoxicosis. It represents an analysis of data obtained on 294 patients with toxic goiter on whom subtotal thyroidectomy was performed and who were followed before and after operation in the endocrine clinic of the Presbyterian Hospital.

## FOLLOW-UP STUDY

This study covers the ten year period 1930 to 1939. During this time 548 patients who had been operated on for toxic goiter reported to the clinic. Of this number, 208 were unsuitable for this study. Some of them had had only one hemithyroidectomy and had then disappeared from observation. Others had been operated on in another clinic, and their course of illness before the operation, the diagnosis and the extent of the thyroidectomy were not well known. We also excluded 46 patients who had been followed up for less than three months after operation. This leaves 294 patients who were known to have had a subtotal thyroidectomy and who were followed up more than three months after operation.

An attempt was made to see every patient at two to three month intervals for the first year after operation. After the first year, as many patients as possible

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From the endocrine clinic, Presbyterian Hospital, and the Department of Medicine, University of Illinois College of Medicine.

1. Thompson, W. O.; Morris, A. E., and Thompson, P. K.: Thyrotoxicosis Following Subtotal Thyroidectomy for Exophthalmic Goiter, *Arch. Int. Med.* **46**: 946-978 (Dec.) 1930.

TABLE 1.—Course of the Basal Metabolic Rate in the Thirty-Nine Patients Who Were Thyrotoxic After Subtotal Thyroidectomy \*

Patient †		Age at		Basal Metabolic Rate		Summary of Basal Metabolic Rates After Discharge	
		Time of Operation, Yr.	At Time of Admission to Hospital	Just Before Operation	At Time of Discharge from Hospital		
No.	Sex						
1	♀	34	+57	+22 †	+ 2 † (12)	+31 (70); +18 (170); +15 (177); +9 (213), pregnant; +28 (229); +23 (243); +25 (264); +17 (301)†; +20 (334)†; +28 (317); +6 (608)†	
2	♂	57	+75	+32 †	+36 † (7)	+26 (50)†; +38 (79)†; +37 (135); +10 (193); +12 (338); +48 (459); +27 (531); +6 (557); +3 (673); —1 (765)†; —5 (837);	
3	♀	35	+44	+28 †	+ 0 † (33)	+10 (37)†; +13 (77); +25 (161); +25 (194); +17 (268)†; +20 (310)†; +19 (351)	
4	♀	35	+50	+50 †	.....	+83 (2,078); +40 (2,139)†; +25 (2,193)†; +35 (2,201); +51 (2,299)†	
5	♀	16	+ 7 †	— 2 †	+ 4 † (7)	+1 (17); +3 (69); —1 (111); +3 (174); +1 (205); +11 (494)†; +2 (504); —4 (809); —7 (1,162); +1 (1,491); +1 (1,498); +25 (1,786); +32 (1,792); +19 (1,813)†; +7 (1,872)†; +17 (1,906)†; +19 (1,940)†; +12 (1,982)†; +5 (2,042); +3 (2,129)	
6	♂	42	+54 †	+18 †	+11 † (11)	+23 (36); +47 (13); +21 (99)†; +7 (130)†; +7 (165)†; +15 (210); +20 (247); +37 (319); —7 (312)†; +1 (345)†; +35 (303); +35 (565); +19 (573)†	
7	♀	38	+71	+12 †	+12 † (7)	+16 (25); +0 (104); —19 (165); —14 (191)†; +4 (325); —10 (355); +22 (1,272); +23 (1,295); +29 (2,579); +30 (3,317); +24 (3,351)†	
8	♀	18	+64 †	+25 †	— 1 † (13)	0 (14)†; +29 (77); +23 (135); +21 (167); +10 (239); +10 (351)	
9	♀	35	+10 †	+10 †	.....	+26 (33); +66 (91); +31 (111)†; +71 (161)	
10	♀	28	+48	+32 †	+30 † (9)	See chart 2	
11	♀	43	+18	+31 †	+27 † (12) +14 † (15)	See chart 5	
12	♀	41	+38 †	+38 †	+ 9 † (12)	See chart 6	
13	♀	49	+17	— 2 †	.....	+22 (24); +23 (61); +15 (300); +17 (543); +3 (925); +4 (1,827)	
14	♀	38	+26 †	+26 †	.....	+27 (537); +13 (651); +27 (769); +19 (785); +23 (912); +23 (1,022); +19 (1,179); +25 (1,272); admission to hospital; —3 (1,283); —2 (1,254)†; —7 (1,287)†; subtotal thyroidectomy; —4 (1,321); +3 (1,361); —6 (1,181); +10 (2,135)	
15	♀	15	+ 9	+13 †	.....	See chart 3	
16	♂	33	+18 †	+33 †	+30 † (10)	0 (30)†; +7 (55); +16 (56); +33 (225); +21 (283); +21 (574)	
17	♀	20	+31	— 3 †	+ 9 † (7)	+19 (104); +15 (199)†; +12 (297)†; +17 (126)†; +13 (176)†; +31 (536); +34 (578); +38 (613)	
18	♀	48	+33 †	+20 †	.....	+17 (45); +13 (209); +19 (231); +14 (291)†; +15 (388); +21 (420); +30 (521); +35 (577)†; +35 (622); +27 (812)	

19	Q	18	+52 ‡	+32 ‡	+20 ‡ (7)	+23 (23); -2 (84)†; +3 (126)†; +15 (147)†; +15 (175)†; +18 (280); +23 (323); +13 (434)†; +28 (539); +9 (609)†; -1 (859)†; -1 (984)†; -3 (1,068)†; -2 (1,195)†; +4 (1,720); +1 (1,859); +3 (2,316)
20	Q	30	+49	+31 ‡	+ 8 ‡ (7)	+19 (39); +18 (90); +17 (222)†
21	Q	45	+55 ‡	+37 ‡	.....	+13 (46); +34 (67); +39 (100); +14 (128)†; +29 (195); +12 (231); +5 (280)†; +18 (368); +9 (459); +6 (554); +2 (918); 0 (1,300)
22	Q	44	+55	+35 ‡	+21 ‡ (4)	+21 (38); +31 (53); +13 (77); +6 (131)†; -1 (204)†; +22 (279); +27 (357); -7 (431)†; +3 (521)†; -7 (713)†; -4 (776)†; +3 (907)‡; +6 (952)§
23	♂	50	+18	+10 ‡	.....	Admission to hospital; +39 (181); +35 (182); +43 (183)†; +11 (186); +40 (188); +26 (198)†; +29 (211); subtotal thyroidectomy; +1 (220); -7 (318); +6 (636); +1 (951); -11 (1,014)
24	Q	41	+32	+18 ‡	.....	+17 (157); +17 (192); +18 (254); +18 (2,100); +36 (2,104); -4 (2,146)†; -7 (2,171)†; -15 (2,209); -3 (2,230)
25	Q	50	+63	+31 ‡	+12 ‡ (7)	See chart 4
26	Q	12	+43	+25 ‡	- 2 ‡ (6)	See chart 1
27	Q	40	+71 ‡	+79 ‡	+20 ‡ (10)	+37 (150)
28	Q	17	+52	+17 ‡	+ 2 ‡ (7)	Admission to hospital; +35 (678); +31 (679); +30 (680); +31 (682); +15 (689)†; +7 (712)†; subtotal thyroidectomy; +6 (725)†; +17 (822); +6 (882)†; 0 (850); +2 (1,164); -5 (1,898); -4 (2,324)
29	Q	17	+62	+59 ‡	+17 ‡ (8)	+37 (45); +28 (76)†; +23 (131); +68 (195)†
30	Q	20	+47	+28 ‡	+ 6 (10)	+29 (95); +27 (144); -12 (1,209)
31	♂	35	+51	+35 ‡	+11 ‡ (8)	+17 (89); +22 (138); +6 (187)†; +31 (257); +35 (517); +10 (741); +11 (797)
32	Q	29	+62	+18 ‡	+23 ‡ (8)	+30 (76); +21 (97)
33	Q	58	+41 ‡	+17 ‡	+19 ‡ (11)	+35 (107); +18 (158); +11 (219); +11 (882)
34	♂	56	+28	+ 7 ‡	+ 8 ‡ (8)	+24 (35)†; +27 (104)†; +7 (134)†; +25 (181)†; +35 (191)†; +21 (333)†; +24 (454)†; +32 (762)†
35	Q	52	+69	+11 ‡	+ 1 ‡ (7)	+24 (47); +15 (118); -8 (163)†; -8 (313)†; +20 (794)
36	Q	57	+76	+57 ‡	+20 (9)	-9 (16); +11 (72); +17 (89); +28 (140); +21 (201)
37	Q	21	+44	+28 ‡	+13 ‡ (7)	+22 (130); +32 (172); +21 (308); +34 (268); +32 (271); +28 (278); +15 (281); +19 (292); +15 (313); +13 (327); +20 (331); +16 (341); +1 (347); 0 (389); +3 (412); +1 (738); +8 (1,398)
38	Q	10	+56 ‡	+24 ‡	+19 ‡ (7)	+26 (60); +1 (134)†; +25 (155); +6 (214)†; -10 (311)†; -2 (540)†; -10 (810); -19 (908); -7 (1,170); -15 (1,825)
39	Q	27	+68	+31 ‡	+29 ‡ (12)	+20 (72); +12 (128); +7 (185)†; -9 (240)†, pregnant; +20 (335); +26 (369)†; +32 (404); +20 (440)†; -15 (1,825)

second thyroidectomy

\* This table gives only an outline of the variation in the basal metabolic rate, expressed as the percentage of the normal rate. In most instances, many more determinations were done. The figures in parentheses denote the number of days after operation.  
† In patients 10 and 13 the diagnosis was toxic adenoma and in the remainder exophthalmic goiter.  
‡ Basal metabolic rate determined during medication with iodine.  
§ Basal metabolic rate determined during medication with thyroid.

were observed at intervals of six months to one year. Patients who were not completely well because of persistence or recurrence of the disease, vocal cord paralysis, parathyroid tetany, postoperative hypothyroidism or some other complication were observed at more frequent intervals. The patients were observed for the following lengths of time:

Duration of Follow-Up After Operation	No. of Patients
3 to 11 mo.	99
1 to 3 yr.	125
4 to 7 yr.	53
Over 7 yr.	17

Each time a patient returned to the clinic for examination a determination of the basal metabolic rate was made with the Sanborn-Benedict apparatus and the Aub-Du Bois standards.

#### TYPE OF OPERATION

The subtotal thyroidectomy was usually done in one stage, but in 27 patients (in 8 of whom postoperative thyrotoxicosis developed and in 19 of whom there was no later evidence of postoperative thyrotoxicosis) two hemithyroidectomies were performed several months apart. In 7 patients (6 without and 1 with postoperative thyrotoxicosis) preliminary polar ligations were done to test the patients' ability to withstand surgical manipulation. About 80 per cent of the operations were done by eight surgeons who do a considerable amount of thyroid surgery; the other 20 per cent were distributed among twenty-one surgeons, some of whom do only occasional thyroidectomies. There was, therefore, no standardization of technic, the amount of tissue left in at operation varying with the different surgeons. The amount of thyroid tissue removed, according to the notes made at operation, usually varied from two thirds to nine tenths of the gland.

#### INCIDENCE OF THYROTOXICOSIS FOLLOWING SUBTOTAL THYROIDECTOMY

There were 39 instances of postoperative thyrotoxicosis among the 294 patients (13 per cent). Of these, 37 occurred among 212 patients with exophthalmic goiter (17.5 per cent) and only 2 among 82 patients with toxic adenoma (2.4 per cent). The remaining patients appeared to be cured; that is, they showed no definite signs or symptoms of thyrotoxicosis after operation and their basal metabolic rate was normal or less than normal. The data on the 39 patients thyrotoxic after operation are summarized in table 1.

In evaluating the presence of postoperative thyrotoxicosis, we considered several factors: the presence of clinical signs and symptoms, such as tachycardia; undue nervousness; ease of fatigue; excessive sweating; loss of weight, and persistent elevation of the basal metabolic rate above the normal. (In general, plus or minus 15 per cent was taken as the normal range.) Many patients who had a slight elevation

of the basal metabolic rate at some time following operation were not included in the group of those who had postoperative thyrotoxicosis because other signs and symptoms of the disease were wanting. No patient was considered to be thyrotoxic unless the basal metabolic rate was consistently  $+15$  per cent or higher without iodine therapy.

#### SEVERITY OF POSTOPERATIVE THYROTOXICOSIS

Although 39 patients were thyrotoxic at some time after operation, only 9 failed to show some symptomatic improvement, and in only 3 (patients 4, 9 and 15) was the thyrotoxicosis worse after subtotal thyroidectomy than before. On the basis of basal metabolism determin-

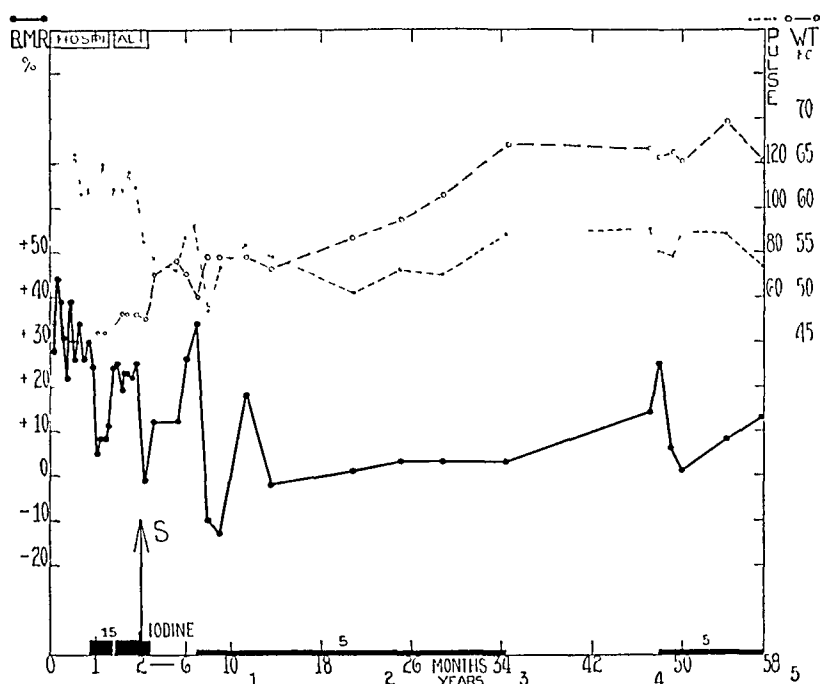


Chart 1 (patient 26).—Typical mild persistence of thyrotoxicosis following subtotal thyroidectomy for exophthalmic goiter. Note that the presence of thyrotoxicosis was masked by the administration of iodine just after operation. This chart shows that iodine may hold the basal metabolic rate within normal limits for many months. The following symbols are used in some or all of the charts: *H*, hospitalization; an arrow and *S*, subtotal thyroidectomy; black areas, periods of treatment with compound solution of iodine U. S. P., with the daily dose in minims indicated above each area, and cross hatched areas, periods of treatment with thyroid with the daily dose in grains indicated above each area.

ations in the 39 patients thyrotoxic after operation, the disease was mild ( $+15$  per cent to  $+29$  per cent) in 54 per cent, moderately severe ( $+30$  per cent to  $+59$  per cent) in 38 per cent and severe ( $+60$  per cent or higher) in 8 per cent, whereas in the same patients before operation it was mild in 10 per cent, moderately severe in 67 per cent and severe in 23 per cent.

## PERSISTENCE AND RECURRENCE OF THYROTOXICOSIS

A distinction was made between patients in whom the disease disappeared after operation and recurred at a later date and those in whom it persisted. The thyrotoxicosis was considered persistent when there was evidence that the disease had not disappeared temporarily after the operation except under the influence of iodine. The thyrotoxicosis was considered recurrent only when there was evidence to show that there was a period after operation when without medication it was not present. On this basis it persisted in 30 patients and recurred in 5, while in 4 instances the data were insufficient to determine the type.

TABLE 2.—*Comparison of Basal Metabolic Rates During Administration of Iodine Shortly After Thyroidectomy\* in Patients Who Were Thyrotoxic and in Those Who Were Not (Exophthalmic Goiter)*

Basal Metabolic Rate, Percentage of the Normal Rate	Patients Thyrotoxic After Operation		Patients Not Thyrotoxic After Operation	
	Number	Percentage	Number	Percentage
+30 or over.....	3	10.3	7	4.8
+25 to +29.....	1	3.5	5	3.5
+20 to +24.....	5	17.2	11	7.6
+15 to +19.....	2	6.9	16	11.0
+10 to +14.....	6	20.7	22	15.2
+ 5 to + 9.....	5	17.2	27	18.6
0 to +14.....	5	17.2	21	14.5
— 5 to —1.....	2	6.9	19	13.1
—10 to —6.....	0	0.0	12	8.3
Below —11.....	0	0.0	5	3.5

\* Six to twelve days afterward in most instances.

## ONSET OF PERSISTENT THYROTOXICOSIS

Thompson and associates<sup>1</sup> have previously shown that when toxic goiter disappears after subtotal thyroidectomy the basal metabolic rate tends to fall to within normal limits ten to fourteen days after operation during the administration of iodine and that when the operation fails to cure the disease the rate tends to remain above + 15 per cent in about 40 per cent of cases. A similar percentage of patients show the same amount of elevation in the present series (table 2), but there is less difference between those with postoperative thyrotoxicosis and those without postoperative thyrotoxicosis, probably because the basal metabolic rates were determined sooner after operation in this series than in that of Thompson and associates. In those patients whose metabolic rate was normal during the administration of iodine at the time of discharge from the hospital, the persistence was usually first noticed shortly after iodine was discontinued.

## COURSE OF PERSISTENT THYROTOXICOSIS

During the time of observation the disease disappeared without any treatment except iodine in 11 (37 per cent) of the 30 patients in whom thyrotoxicosis persisted; that is, these patients ceased to require treatment to maintain their metabolism within normal limits. These remissions took place from about four months to about three years after operation. In the remaining 19 patients the disease persisted for the duration of the follow-up study or until a second thyroidectomy was done. Four of them showed a tendency to improve gradually. In other words, the level to which iodine depressed the metabolism or the level to which the metabolism rose after omission of iodine gradually decreased.

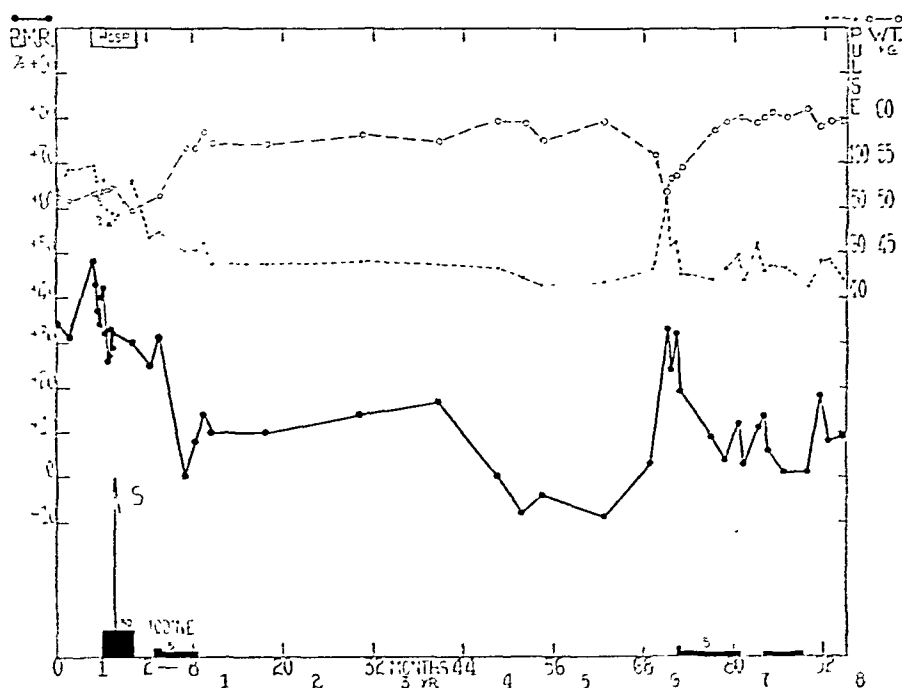


Chart 2 (patient 10).—Recurrence of toxic adenoma about six years after subtotal thyroidectomy and control of thyrotoxicosis by iodine until it finally disappeared. The recurrence was associated with marked regeneration of thyroid tissue. For explanation of the symbols see chart 1.

The remaining 15 patients showed no tendency to improve under iodine therapy, and 4 of them gradually became worse, as judged by the level of metabolism.

## ONSET AND COURSE OF RECURRENT THYROTOXICOSIS

As previously stated, a true recurrence was noted in 5 patients. Two of them were well after operation until the onset of the recurrence, between one and three years after operation (patient 7) and between four and five years after operation (patient 5), respectively. The



other 3 patients (15, chart 3; 25, chart 4, and 10, chart 2) had some residual symptoms of thyrotoxicosis, which persisted from three and a half to eight months after operation, after which interval a remission took place, and they were then well until the onset of the recurrence, about two, four and a half and six years after thyroidectomy, respectively.

Of the five recurrences of thyrotoxicosis, one lasted twenty-two months, until a second thyroidectomy was done; one lasted somewhere between five and fourteen months and disappeared spontaneously, and three lasted for the duration of the follow-up study (eight months, two years and three and one-half years, respectively).

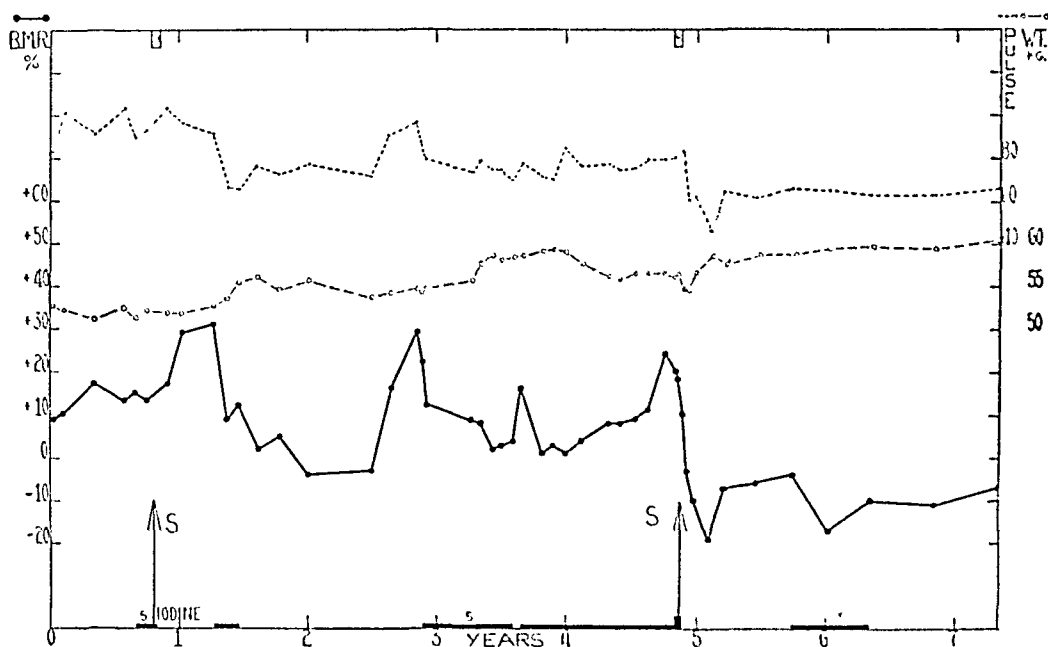


Chart 3 (patient 15).—Spontaneous remission of exophthalmic goiter between six and ten months after subtotal thyroidectomy and a later recurrence of the disease between twenty and twenty-two months after operation. The recurrence was accompanied by marked regeneration of thyroid tissue and finally required a second thyroidectomy. For explanation of the symbols see chart 1.

#### CAUSES OF POSTOPERATIVE THYROTOXICOSIS

*Miscellaneous Factors.*—In tables 3 to 7 data on age incidence, sex distribution, duration of symptoms at the time of operation, basal metabolic rate at the time of admission to the hospital and size of the thyroid gland before operation in the patients with exophthalmic goiter who were thyrotoxic after operation are compared with similar data on those who were not. The figures for the two groups are about the same, the only difference being that the average duration of symptoms was somewhat less for those with postoperative thyrotoxicosis. An analysis of these

factors in 190 patients with exophthalmic goiter studied in Boston also failed to show any clearcut difference between the two groups.

In our experience postoperative thyrotoxicosis occurs infrequently among patients with so-called toxic adenoma, there being only 2 instances

TABLE 3.—*Age of Patients with Exophthalmic Goiter at the Time of Operation*

Age, Yr.	Patients Thyrotoxic After Operation		Patients Not Thyrotoxic After Operation	
	Number	Percentage	Number	Percentage
Under 20.....	5	13.5	10	5.7
20 to 29.....	5	13.5	27	15.4
30 to 39.....	9	24.3	57	32.6
40 to 49.....	11	29.7	54	30.9
50 to 59.....	7	18.9	20	11.4
60 or over.....	0	0.0	7	4.0
	37		175	
Average age.....		37.9		38
Highest age.....		57		74
Lowest age.....		12		13

TABLE 4.—*Sex of Patients with Exophthalmic Goiter*

	Patients Thyrotoxic After Operation		Patients Not Thyrotoxic After Operation	
	Number	Percentage	Number	Percentage
Male.....	6	16.2	35	20.0
Female.....	31	83.8	140	80.0
	37		175	

TABLE 5.—*Duration of Symptoms at the Time of Operation in Patients with Exophthalmic Goiter*

Duration	Patients Thyrotoxic After Operation		Patients Not Thyrotoxic After Operation	
	Number	Percentage	Number	Percentage
Less than 6 months.....	11	29.7	58	33.1
6 to 11 months.....	10	27.0	41	23.4
1 to 2 years.....	6	16.2	25	14.3
Over 2 years.....	9	24.3	40	22.9
Unknown.....	1	2.7	11	6.3
	37		175	
Shortest duration.....		1 month		3 weeks
Longest duration.....		5 years		17.5 years
Average duration.....		18.6 months		22.7 months

among 82 patients in the present series. The question of the accuracy of the diagnosis in these 2 instances naturally arises. Plummer did not find any instances of postoperative thyrotoxicosis in a large series of patients with toxic adenoma.<sup>2</sup>

2. Plummer, H. S.: The Function of the Thyroid Gland Containing Adenomatous Tissue, *Tr. A. Am. Physicians* **43**:159, 1928.

*Possible Precipitating Factors.*—Pemberton<sup>3</sup> expressed the belief that infections, overwork, worry, fright, shock, pregnancy and operations are important factors in recurrences. Berlin and Gargill<sup>4</sup> concluded from a study of 11 recurrences of the disease that inadequate thyroidectomy played less of a role than other factors, such as psychic trauma, infections, pregnancy, tuberculosis, the menopause and the personality of the patient. In only a few instances could we find such factors operative

TABLE 6.—*Basal Metabolic Rate at the Time of Admission to the Hospital in Patients with Exophthalmic Goiter*

Basal Metabolic Rate, Percentage of Normal *	Patients Thyrotoxic After Operation		Patients Not Thyrotoxic After Operation	
	Number	Percentage	Number	Percentage
Below +40.....	9	24.3	70	40.0
+40 to +49.....	9	24.3	28	16.0
+50 to +59.....	10	27.0	29	16.6
+60 and over.....	9	24.3	48	27.4
	37		175	
Highest rate.....		+76		+113
Lowest rate.....		+ 7		— 2
Average rate.....		+48.5		+ 46.1

\* In a few cases the basal metabolic rate was determined during the administration of iodine.

TABLE 7.—*Size of the Thyroid Before Operation in Patients with Exophthalmic Goiter*

Size of Thyroid	Patients Thyrotoxic After Operation		Patients Not Thyrotoxic After Operation	
	Number	Percentage	Number	Percentage
Not enlarged.....	1	2.7	8	4.6
Slightly enlarged.....	11	29.7	48	27.4
Moderately enlarged.....	20	54.0	101	57.7
Markedly enlarged.....	5	13.5	18	10.3
	37		175	

in our patients. Pleurisy with effusion developed in 1 patient (10, chart 2) after an infection of the upper respiratory tract. Coincident with the termination of this infection, elevation of the basal metabolic rate and return of symptoms of fatigue, nervousness and tachycardia

3. Pemberton, J. deJ.: Recurring Exophthalmic Goiter: Its Relation to the Amount of Tissue Preserved in Operation on the Thyroid Gland, *J. A. M. A.* **94**:1483-1489 (May 10) 1930.

4. Berlin, D. D., and Gargill, S. L.: Factors Influencing Persistent and Recurrent Hyperthyroidism, *New England J. Med.* **222**:254-259 (Feb. 15) 1940.

were noticed. In the other 4 patients with recurrence of the disease there was no associated disturbance in the nature of infection, the menopause or unusually upsetting emotional experiences. In 1 patient (19) who had a severe cold accompanied by a sore throat about twice a year, we observed a remission of the disease after it had persisted for two years after thyroidectomy. For the ensuing five years there was no elevation of the basal metabolic rate, although the colds continued unabated. In another patient (2) persistent thyrotoxicosis increased in severity on two occasions during a severe cold, but in each instance the metabolic level promptly reestablished itself when the cold subsided. In only 3 patients was postoperative thyrotoxicosis complicated by preg-

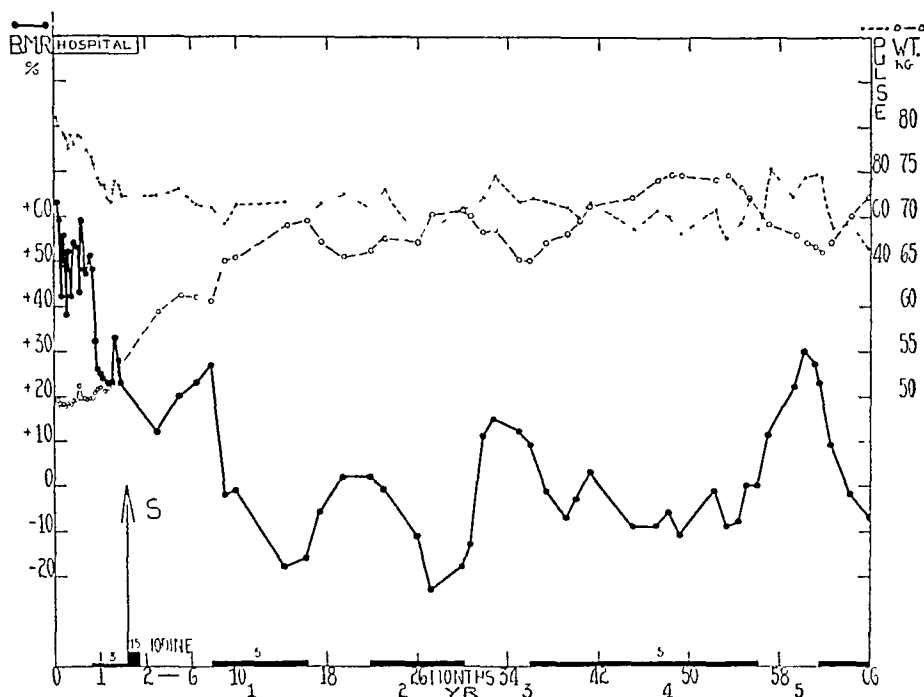


Chart 4 (patient 25).—Persistence and recurrence of exophthalmic goiter. The disease persisted for at least six months after subtotal thyroidectomy. The patient was then well for nearly five years, but during this time the levels of the basal metabolism with and without iodine gradually rose. A recurrence took place about five years after operation. For explanation of the symbols see chart 1.

nancy. Two of them (patients 1 and 39) had slightly lower metabolic rates during pregnancy, but after delivery the rates reverted to the prepartum level. A third patient (28) became more thyrotoxic during pregnancy.

Our data suggest that infections, unusually upsetting emotional experiences, pregnancy and the menopausal syndrome are not important factors in the onset of persistent and recurrent thyrotoxicosis. If they play any role at all, it is probably merely as precipitating factors.

## AMOUNT OF THYROID TISSUE PALPABLE AFTER OPERATION

Cattell and Morgan<sup>5</sup> reported that palpation of the thyroid gland after operation is frequently unreliable because the scar tissue resulting from the previous thyroidectomy makes it difficult to outline the lateral lobes. In our experience, palpation is difficult only for a few weeks after operation, until induration disappears. In many patients, thyroid tissue can then easily be palpated and can often be observed to regenerate or regress in amount. In table 8 is expressed the maximum amount of thyroid tissue palpable after operation. "Questionable" means that the thyroid tissue was sufficiently difficult to palpate to render its presence open to question. "Definitely" signifies that the tissue could be felt, and

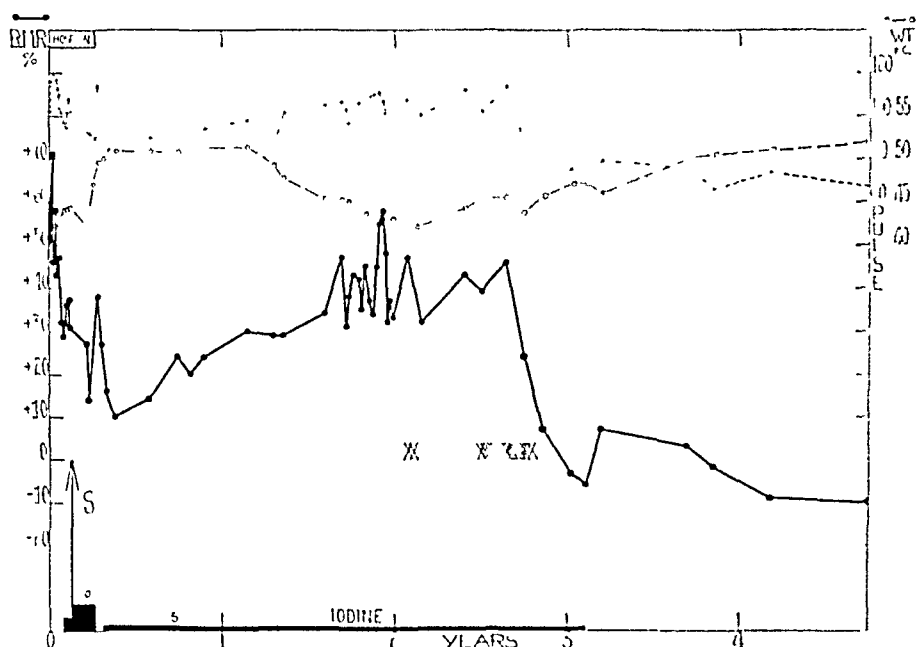


Chart 5 (patient 11).—Persistence of thyrotoxicosis following subtotal thyroidectomy for exophthalmic goiter, with a gradual rise in the metabolic rate during prolonged administration of iodine. A remission took place about three years after operation following roentgen ray therapy. X denotes roentgen ray treatment over the thyroid. For explanation of the other symbols see chart 1.

the mass varied in amount up to 1.5 cm. in diameter. "Considerable" is used to include all masses of thyroid tissue larger than 1.5 cm. in diameter. It is of interest that of 286 patients on whom frequent observations were made, 108 (38 per cent) had sufficient thyroid tissue present to be palpable at some time after operation. The incidence of palpable thyroid tissue and of regeneration of thyroid tissue was greater in

5. Cattell, R. B., and Morgan, E. S.: Recurrent Hyperthyroidism, Surg., Gynec. & Obst. 68:347-351 (Feb.) 1939.

patients who were thyrotoxic after operation than in those who were not. Thus it may be seen in table 8 that 32 patients (89 per cent) with postoperative thyrotoxicosis had palpable thyroid tissue at some time following operation, as compared with 76 (30 per cent) of those without thyrotoxicosis. Only 4 patients in the former group had no palpable tissue, and in each of these patients thyrotoxicosis was mild.

Similarly, regeneration of thyroid tissue was noted much more frequently among patients with postoperative thyrotoxicosis. Of 31 patients on whom frequent observations were made, 23 (74 per cent) showed some regeneration, while of 230 patients without postoperative thyrotoxicosis, only 34 (15 per cent) showed regeneration of thyroid tissue. That thyrotoxicosis, even of a severe nature, may occur in the presence of a small amount of thyroid tissue or in the absence of any palpable thyroid tissue has been pointed out by Haines and Pemberton,<sup>6</sup> Moor-

TABLE 8.—*Maximum Amount of Thyroid Tissue Palpable \* After Operation in Patients with Toxic Adenoma and with Exophthalmic Goiter*

	Patients Thyrotoxic After Operation		Patients Not Thyrotoxic After Operation	
	Number	Percentage	Number	Percentage
Palpation attempted.....	36		250	
Palpable tissue absent.....	4	11.1	174	69.6
Palpable tissue present.....	32	88.9	76	30.4
Questionable amount of tissue present....	2	6.2	17	22.4
Definite amount of tissue present.....	15	46.9	38	50.0
Considerable amount of tissue present....	15	46.9	21	27.6

\* For definition of the terms used to describe the amount of tissue palpable see the section in the text headed "Amount of Thyroid Tissue Palpable after Operation."

head<sup>7</sup> and Phemister and Delaney.<sup>8</sup> However, such occurrences are the exception rather than the rule. In general, the presence of palpable amounts of thyroid tissue after operation is fairly strong presumptive evidence of the presence of thyrotoxicosis.

#### RELATION OF POSTOPERATIVE THYROTOXICOSIS TO THE AMOUNT OF THYROID TISSUE LEFT IN AT OPERATION

Bowers<sup>9</sup> expressed the opinion that the amount of thyroid tissue left by the surgeon determines the incidence of persistent and of recurrent thyrotoxicosis. His study of 302 patients showed that the surgeon with

6. Haines, S. F., and Pemberton, J. deJ.: Control of Hyperthyroidism Following Partial Thyroidectomy, *Arch. Int. Med.* **57**:1104-1114 (June) 1936.

7. Moorhead, T. G.: Athyroid Thyrotoxicosis, *Irish J. M. Sc.*, February 1940, pp. 80-81.

8. Phemister, D. B., and Delaney, P. A.: Thyrotoxicosis Continuing After Extreme Operative, Iodine, and Roentgen Therapy, *J. A. M. A.* **100**:568 (Feb. 25) 1933.

9. Bowers, R. F.: Recurrent Toxic Goiter, *West. J. Surg.* **47**:536-542 (Sept.) 1939.

the lowest percentage of recurrences had the highest percentage of post-operative myxedema. In the series of 190 patients with exophthalmic goiter followed-up in Boston<sup>1</sup> the incidence of postoperative thyrotoxicosis was 14.4 per cent for three surgeons doing a large amount of thyroid surgery and 36.3 per cent for ten other surgeons who did relatively few thyroidectomies. Table 9 shows the incidence of post-operative thyrotoxicosis according to surgeons for the present study. It can be seen that the incidence among eight surgeons doing a large amount of thyroid surgery was 14.5 per cent, whereas for the surgeons doing thyroidectomies occasionally it was 28.3 per cent. We know from observation that surgeon B, who has the lowest incidence of post-

TABLE 9.—*Incidence of Postoperative Thyrotoxicosis According to Surgeons Performing the Thyroidectomies*

Surgeon	Number of Patients Operated On	Patients Thyrotoxic After Operation	
		Number	Percentage
A.....	43	7	16.3
B.....	30	1	3.3
C.....	21	4	19.0
D.....	19	4	21.1
E.....	19	3	15.8
F.....	13	2	15.4
G.....	9	1	11.1
H.....	8	2	25.0
21 other surgeons.....	46	13	28.3
Unknown.....	1	0	0.0
Total.....	212	37	
Surgeons doing the most thyroid surgery.....	166	24	14.5
21 surgeons doing only occasional thyroidectomies.....	46	13	28.3
Number Percentage			
Patients with permanent paralysis of one vocal cord.....		23	9.5
Patients with permanent parathyroid tetany.....		11	3.7

operative thyrotoxicosis, does a rather extensive subtotal thyroidectomy. It was also true in the Boston series that the more experienced surgeons performed more extensive thyroidectomies and had the smallest incidence of postoperative thyrotoxicosis. Many other observers<sup>10</sup> have

10. Else, J. E.: Prevention of Recurrent Goiter, *S. Clin. North America* **8**: 1375-1394 (Dec.) 1928. Gilman, P. K., and Kay, W. E.: Certain Advantages of Total Thyroidectomy in Selected Cases of Thyrotoxicosis of the Exophthalmic Type, *Am. J. M. Sc.* **175**:350-360 (March) 1928. Lahey, F. H.: Review of Another Year's Work with Thyroid Disease, *Boston M. & S. J.* **190**:153-156 (Jan.) 1924. Elliott, C. A.: The Control of Hyperthyroidism by Thyroidectomy: Results in One Hundred Cases, *J. A. M. A.* **89**:519-522 (Aug. 13) 1927. Smith, L. W.; Clute, H. M., and Streider, J. W.: The Results in One Hundred Consecutive Cases of Hyperthyroidism Operated Upon, *Surg., Gynec. & Obst.* **46**:325-331 (March) 1928. Waits, C. E.: Preoperative and Postoperative Studies in Goiter, *J. M. A. Georgia* **11**:355 (Sept.) 1922. Clute, H. M.: Hyperthyroidism Persisting After Thyroidectomy: The Necessity for Postoperative Examinations in Toxic Goiters, *S. Clin. North America* **6**:691-694 (June) 1926. Cattell and Morgan.<sup>5</sup>

stated that one of the chief causes of thyrotoxicosis following subtotal thyroidectomy is the removal of too little thyroid tissue. This is supported in our series by the fact that there was no outstanding difference before operation between the patients who were thyrotoxic after operation and those who were not and perhaps to some extent by the greater percentage of patients who had palpable thyroid tissue after operation among those with thyrotoxicosis than among those without thyrotoxicosis. In 1 patient (9) in whom there was a considerable amount of thyroid tissue palpable after operation the surgeon was forced to terminate the operation because of hemorrhage after a little more than a third of the gland had been removed. Within three months after operation the thyrotoxicosis was more severe than before operation. In cases of this kind it is quite obvious that the removal of more tissue would produce a better result.

Inadequate removal of thyroid tissue will not explain all the cases of persistence however. It seems to us of more than passing interest that the incidence of persistence of the disease was about the same for the more experienced surgeons in the Boston series as for those in the Chicago series, particularly since these two groups' of patients were studied at different times and in entirely different parts of the country, one in which simple goiter is rare and one in which it is prevalent. We have seen patients in whom the disease persisted with rapid and extensive regeneration of thyroid tissue in spite of the removal of all but a small remnant of the thyroid gland. Under such circumstances the cause of the disease must still be active and perhaps is driving the gland to increased activity.

Recurrence of the disease presents an interesting problem. The patients who showed this phenomenon were free from the disease for a period of six months to five years after thyroidectomy, indicating that the thyroidectomy had been adequate. In every case there was regeneration of thyroid tissue at the time of recurrence. Similarly, in all but 8 patients with persistence of the disease regeneration of thyroid tissue was noted. It would thus appear that whereas in some patients showing persistence the cause of the disease remains active in spite of thyroidectomy, in patients showing recurrence the cause becomes quiescent and after a variable period becomes active again. The course of the disease in patients with persistence and recurrence, in particular its tendency to show remissions and relapses in association with fluctuations in the rate of metabolism, resembles the course of the untreated disease. The problem that continues to puzzle us is why the cause of the disease should apparently become quiescent in such a large percentage of patients at the time of a subtotal thyroidectomy, thus permitting a cure.



## TREATMENT

The effect of iodine on the course of the disease was determined in 33 of the 39 patients thyrotoxic after operation. In 22 the disease was controlled by administration of iodine either during the period of observation or until remission of the disease took place, after which no further treatment was necessary. In 11 patients the disease could not be controlled with iodine. That is, the basal metabolic rate remained at a level of  $+15$  per cent or higher in spite of prolonged administration of iodine. Six of these patients had second subtotal thyroidectomies, with termination of the thyrotoxicosis in 4. In 1 patient it is too soon after operation to tell whether the disease is still present or not, and 1 patient had a

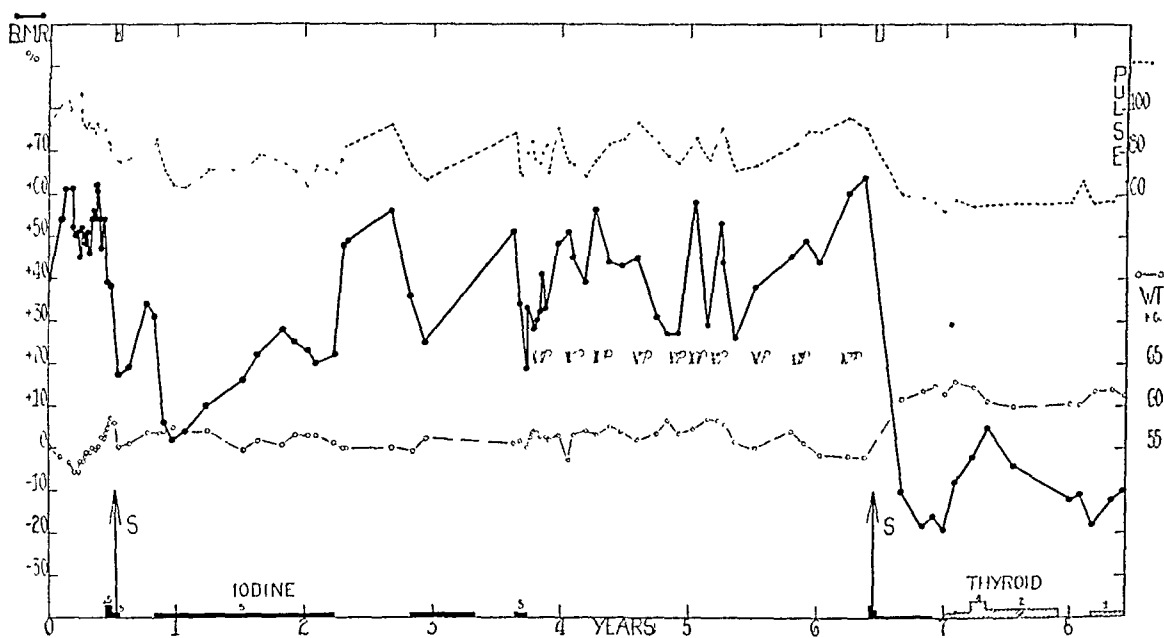


Chart 6 (patient 12).—Persistence of exophthalmic goiter, with a great deal of regeneration of thyroid tissue in spite of roentgen ray treatment over the pituitary and the administration of iodine. The patient became myxedematous after a second subtotal thyroidectomy. Symbols in center of chart which look like *XP* indicate roentgen ray treatment over the pituitary. For explanation of the other symbols see chart 1.

second persistence which lasted from three to four months and was then followed by a spontaneous remission. Of the 5 others in whom the disease could not be controlled with iodine, a second thyroidectomy was contraindicated in 1 because of vocal cord paralysis resulting from the first operation (patient 11). She was given roentgen ray therapy over the thyroid gland, with prompt and permanent remission. The other 4 patients have been advised to have a second thyroidectomy.

In general, in our experience, about two thirds of patients in whom thyrotoxicosis persists or recurs after operation require no treatment

other than the prolonged use of iodine to hold the disease in check or to control it until permanent remission takes place. In view of this relatively large percentage, iodine therapy should be given a fair trial in all patients. In about one third of the patients the disease cannot be controlled with iodine. Of 11 patients in this category, all but 1 showed marked regeneration of thyroid tissue. It is our practice under such circumstances to advise a second thyroidectomy. Roentgen ray therapy is reserved for those patients in whom some factor, such as paralysis of the recurrent laryngeal nerve on the unaffected side makes further surgical intervention inadvisable and for those who refuse to have further surgical treatment.

That in many patients thyrotoxicosis after operation can be controlled with iodine has received some attention. Berlin and Gargill<sup>4</sup> stated that they give it a fair trial in all patients except those in whom there is marked regeneration of thyroid tissue. Haines<sup>11</sup> found that of 488 patients with recurrent or persistent exophthalmic goiter who were examined at the Mayo Clinic, 123 (25 per cent) were treated satisfactorily with medical management only. In our own experience the disease was adequately controlled with iodine in a larger percentage of patients (about 67 per cent).

#### RESULTS OF SUBTOTAL THYROIDECTOMY IN VARIOUS CLINICS

In 1930 one of us (W. O. T.) and associates<sup>1</sup> pointed out that the incidence of thyrotoxicosis following subtotal thyroidectomy as reported from various clinics previous to that time varied from about 0.25 to 25 per cent, many of the reports showing an incidence of 5 to 7 per cent. It was pointed out that variations in these figures were in part due to the different types of follow-up study used by different authors.

It is of interest that the incidence of postoperative thyrotoxicosis among 190 patients with exophthalmic goiter followed at the Massachusetts General Hospital from 1920 to 1929 by Thompson, Morris and Thompson<sup>1</sup> was 19.5 per cent, practically the same as the incidence of 17.5 per cent for patients with exophthalmic goiter in the present series. The type of follow-up study used in both investigations was the same.

Of 4,956 patients with hyperthyroidism undergoing thyroidectomy from 1928 to 1937 at the Lahey Clinic, Boston, 2.4 per cent were operated on for persistence and 3.7 per cent for recurrence of the disease.<sup>12</sup> Joyce, in summarizing the results of thyroid surgery at the

11. Haines, S. F.: *The Use of Iodine in Recurrent Exophthalmic Goiter*, West. J. Surg. **42**:449-455 (Aug.) 1934.

12. Cattell, R. B., and Perkin, H. J.: *Recurrent Hyperthyroidism*, West. J. Surg. **47**:55-61 (Feb.) 1939. Cattell, R. B.: *The Technic of Secondary Thyroidectomy for Recurrent or Persistent Hyperthyroidism*, S. Clin. North America **19**:573-578 (June) 1939. Cattell and Morgan.<sup>5</sup>

Portland Clinic,<sup>13</sup> Portland, Ore., stated that the incidence of recurrence among patients operated on for goiter was 3.6 per cent for the adenomatous and 5.7 per cent for the hyperplastic variety. Of 108 patients operated on by Gillette,<sup>14</sup> 7, or 6.5 per cent, were reported to show recurrence. Buchbinder<sup>15</sup> reported that of 582 consecutive patients undergoing thyroidectomy by Dr. H. M. Richter, 3.3 per cent required a second operation. Young<sup>16</sup> found that 2.7 per cent of 2,064 patients required a second operation. In these reports the incidence of postoperative thyrotoxicosis is based on the number of patients requiring a second thyroidectomy. There were only 10 such patients in our series, all with exophthalmic goiter, so that if this was the only criterion of postoperative thyrotoxicosis the incidence would be reduced to 3.4 per cent. The incidence of postoperative thyrotoxicosis is much higher when patients are followed up for long periods with basal metabolism determinations and physical examinations, as in the present study. If left to their own judgment many patients still thyrotoxic after operation would feel so much better than before that they would consider themselves cured.

Hagen<sup>17</sup> estimated that the combined incidence of persistence and recurrence of the disease in a series of 500 patients whom he had operated on for toxic goiter was about 20 per cent. Bowers<sup>9</sup> reported the incidence of recurrence was 6.6 per cent among 302 patients with toxic goiter whom he had observed throughout the course of their illness. Coller and Potter<sup>18</sup> in a follow-up study, conducted partly by letter one to five years after operation, found an incidence of recurrence of 4.8 per cent among 267 patients with exophthalmic goiter and no recurrences among 273 patients with toxic adenoma. Hane,<sup>19</sup> after a follow-up study conducted by letter of 62 patients operated on for exophthalmic goiter, concluded that 3.2 per cent had recurrence and 4.8 per cent persistence of the disease. None of these authors specified the type of operation.

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13. Joyce, T. M.: Thyroid Surgery at the Portland Clinic, *Ann. Surg.* **94**: 563-567 (Oct.) 1931.

14. Gillette, N. W.: Recurrent Hyperthyroidism, *West. J. Surg.* **45**:504-510 (Sept.) 1937.

15. Buchbinder, W. C.: Some Cases of So-Called "Recurrent Thyrotoxicosis," *M. Clin. North America* **14**:1267-1276 (March) 1931.

16. Young, T. O.: Recurrent and Continuing Hyperthyroidism, *Am. J. Surg.* **39**:104-111 (Jan.) 1938.

17. Hagen, O. J.: Recurrent Thyrotoxicosis After Thyroidectomy, *Minnesota Med.* **22**:828-831 (Dec.) 1939.

18. Coller, F. A., and Potter, E. B.: The End Results of Thyroidectomy, *Ann. Surg.* **94**:568-581 (Oct.) 1931.

19. Hane, R. L.: Recurrent Hyperthyroidism, *J. Indiana M. A.* **33**:675-677 (Dec.) 1940.

Clarke and Black<sup>20</sup> recalled 181 patients two and a half years after operation for toxic goiter and found that in "44 per cent there was either a definite persistence or a recurrence of the condition," the patients not having obtained sufficient relief to consider themselves well. Of 171 patients followed by Pool and Garlock<sup>21</sup> for six months to nine years after resection of the thyroid gland in one stage for toxic goiter, 9.4 per cent had recurrences. Smith<sup>22</sup> found that 13 per cent of 75 patients with toxic diffuse goiter had hyperthyroidism after subtotal thyroidectomy. Of 804 patients followed six months to fourteen years after thyroidectomy for hyperthyroidism, McQuillen and Breidenback<sup>23</sup> considered 5.6 per cent to have recurrences, although some of the patients had a recurrence of the goiter only. In Berlin and Gargill's series<sup>4</sup> of 235 patients, all of whom had subtotal thyroidectomies, there were 3.0 per cent with persistence and 2.1 per cent with recurrence of the disease. In a five year follow-up study of 97 patients operated on for thyrotoxicosis at the Lahey Clinic Clute and Veal<sup>24</sup> reported that 6 had persistent and 6 recurrent thyrotoxicosis, a total incidence of postoperative thyrotoxicosis of 12.3 per cent.

Variations in these figures depend on the frequency and the type of the follow-up study and on the observer's evaluation of the patient when he sees him after operation. Unfortunately, a distinction is not made between persistence and recurrence of the disease in many reports. However, there seems to be general agreement that of all patients having subtotal thyroidectomy for toxic goiter, 2.7 to 6.5 per cent have severe enough postoperative thyrotoxicosis to require a second thyroidectomy.

#### COMMENT

It is of interest that in a group of patients with exophthalmic goiter studied in Chicago, an area in which simple goiter is prevalent, during the period 1930 to 1939, the incidence of postoperative thyrotoxicosis was about the same as that in a group of patients studied in Boston, an area in which simple goiter is rare, from 1920 to 1929. The surgeons performing the thyroidectomies in both series were probably about equally competent, suggesting that the cause of the thyrotoxicosis is not abolished by the

20. Clarke, N. E., and Black, I.: Postoperative Results in Toxic Goiter, *Arch. Int. Med.* **46**:266-282 (Aug.) 1930.

21. Pool, E. H., and Garlock, J. H.: The Surgical Treatment of Exophthalmic Goiter: Late End-Results, *Surg., Gynec. & Obst.* **59**:330-336 (Sept.) 1934.

22. Smith, M. K.: Amount of Thyroid Tissue to be Left in Operations for Diffuse Toxic Goiter, *Ann. Surg.* **108**:563-573 (Oct.) 1938.

23. McQuillen, A. S., and Breidenback, L.: Morbidity Following Goiter Operations, *Ann. Surg.* **106**:169-182 (Aug.) 1937.

24. Clute, H. M., and Veal, J. R.: The End-Results of Surgery in Exophthalmic Goiter, *J. A. M. A.* **99**:642-645 (Aug. 20) 1932.

operation and may continue to be active in spite of it. Both in the Chicago and in the Boston series, the incidence was lower among the patients of the more experienced surgeons than among those whose thyroidectomies were performed by less experienced surgeons. In general, the less experienced surgeons did less complete thyroidectomies. As the thyroidectomy becomes more and more complete, the gland becomes less and less capable of responding to any stimulus to which it may be subjected. The relation between the amount of thyroid tissue and the severity of the thyrotoxicosis is probably modified by the intensity with which the cause of the disease is acting. A few patients show definite persistence of the disease in spite of the presence of only a small amount of palpable thyroid tissue or no palpable tissue at all. That the cause of the disease is still active in patients showing persistence of exophthalmic goiter is also illustrated by the regeneration of thyroid tissue in a fairly large percentage of them. The surprising thing is that a subtotal thyroidectomy ever cures exophthalmic goiter, and yet in over 80 per cent of cases the basal metabolic rate drops to normal or below after this procedure and remains there. In some instances a hemithyroidectomy may cause reduction of the basal metabolic rate to normal. Thus there appears to be a balance of the intensity with which the cause of the disease is acting, the amount of thyroid tissue and the production of active agent by the gland. Exacerbations may occur in the degree to which the cause is acting. Only in this way can recurrence and variations in the intensity of persistence of thyrotoxicosis be explained.

#### SUMMARY AND CONCLUSIONS

Of 294 patients with toxic goiter undergoing subtotal thyroidectomies during the period 1930 to 1939 and followed up from three months to ten years after operation, 39 showed definite clinical evidence of postoperative thyrotoxicosis. Of this number, 37 were among 212 patients with exophthalmic goiter (17.5 per cent) and 2 among 82 patients with toxic adenoma (2.4 per cent).

The thyrotoxicosis was usually less severe than before operation, although in 3 patients it was more severe.

Distinction is made between persistent and recurrent thyrotoxicosis. In 30 patients the thyrotoxicosis was persistent and in 5 recurrent, while in 4 patients the type could not be determined.

In 3 of the 5 patients considered to have recurrent thyrotoxicosis the recurrence was preceded by a persistence and a spontaneous remission of the disease.

In 22 of 33 patients on whom the observation was made it was found that postoperative thyrotoxicosis could be adequately controlled with

iodine alone. In 11 of these patients who had a persistence of the disease, permanent remission was observed between four months and three years after operation.

There was a rough parallelism between the amount of thyroid tissue palpable after operation and the degree of postoperative thyrotoxicosis, although there were important exceptions to this rule. Thus regeneration of thyroid tissue was observed in 74 per cent of patients with postoperative thyrotoxicosis but in only 15 per cent of those without thyrotoxicosis after operation. Of the patients as a whole, regeneration was observed in 22 per cent.

The presence of palpable thyroid tissue after operation is evidence in favor of thyrotoxicosis until proved otherwise.

Two main factors are responsible for thyrotoxicosis following subtotal thyroidectomy for toxic goiter: (1) the failure of the operation to remove the cause of the disease, and (2) the removal of too little thyroid tissue.

Such factors as infections, pregnancy, the menopausal syndrome, worry and fatigue do not seem to play an important role. If related in any way to the onset of the disease, they are certainly no more than precipitating factors.

It is probably desirable to reoperate on all patients with postoperative thyrotoxicosis in whom the basal metabolic rate cannot be held at or near the standard normal level (below  $+15$  per cent) by the administration of iodine.

Postoperative administration of iodine will not prevent the regeneration of thyroid tissue.

The course of postoperative thyrotoxicosis, including its tendency toward remissions and relapses, resembles the course of the untreated disease.

# CARDIOMETRIC STUDIES ON CHILDREN

## III. REPORT OF A CASE OF INCOMPLETE HEART BLOCK DUE TO VAGAL EFFECT \*

WILLIAM POEL

BETHESDA, MD.

Reports on persistent vagal disturbances of the heart mechanism in apparently normal persons with the exception of sinus arrhythmia and bradycardia are exceedingly rare. A survey of the literature revealed only 3 cases of such disturbance.<sup>1</sup>

In a recent study of the electrocardiographic variations of the healthy heart, electrocardiograms and stethograms were made on more than 2,400 apparently normal high school students. The following case of physiologic heart block of vagal origin was the only instance of such a disturbance which was observed. It occurred in a Negro boy who except for this abnormality was clinically normal and entirely free of any sense of physical ill-being or of symptoms which could be related either directly or indirectly to a condition of heart block. Observations made in this case are reported, compared with those of Levy<sup>1a</sup> and Marzahn<sup>1b</sup> and discussed in the light of electrocardiographic changes in the human heart due to experimentally induced vagal effects.<sup>2</sup>

### REPORT OF CASE

*History.*—According to his medical history, a Negro boy aged 15 had never suffered from attacks of rheumatic fever, chorea or heart disease. He had received

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\* Data on which this paper is based were derived from a cooperative investigation by the United States Public Health Service, Division of Public Health Methods; the Cornell University Medical College, Departments of Public Health, Preventive Medicine and Pediatrics; the Milbank Memorial Fund, and the New York City Department of Health. The cooperating agencies have been assisted in carrying out this investigation by the Work Projects Administration for the city of New York, Official Project No. 65-1-97-21, W. P. 24, "Medical Evaluation of Nutritional Status."

1. (a) Levy, R. L.: Partial Heart Block Due to Increased Vagus Action, *Ann. Int. Med.* **12**:1525-1529 (March) 1939. (b) Marzahn, H.: *Clinical Notes on the Question of Functional Heart Block*, *Klin. Wchnschr.* **15**:486-488 (April 4) 1936.

2. (a) Robinson, G. C., and Draper, G.: Studies with the Electrocardiograph on the Action of the Vagus Nerve on the Human Heart. *J. Exper. Med.* **14**:217-233, 1911. (b) Sigler, L. H.: Electrocardiographic Observation on the Carotid Sinus Reflex, *Am. Heart J.* **9**:782-791 (Aug.) 1934. (c) Wiggers, C. J.: *Physiology in Health and Disease*, ed. 2, Philadelphia, Lea & Febiger, 1937, p. 468.

periodic physical check-ups from his father, who is a physician. He had never experienced spells of dizziness, fainting, palpitation of the heart or other symptoms which might be traceable to cardiac dysfunction. At the time of the survey the boy was a member of his school's swimming team. He had always been an active athlete.

*Physical Examination.*—Routine examination revealed the boy to be well nourished and well developed. The stage of physical development was advanced adolescence. The eyes, ears, nose and mouth showed nothing abnormal. The tonsils were normal, and the thyroid was not enlarged. No lymph nodes were palpable. The lungs were normal. The blood pressure was 120 systolic and 80

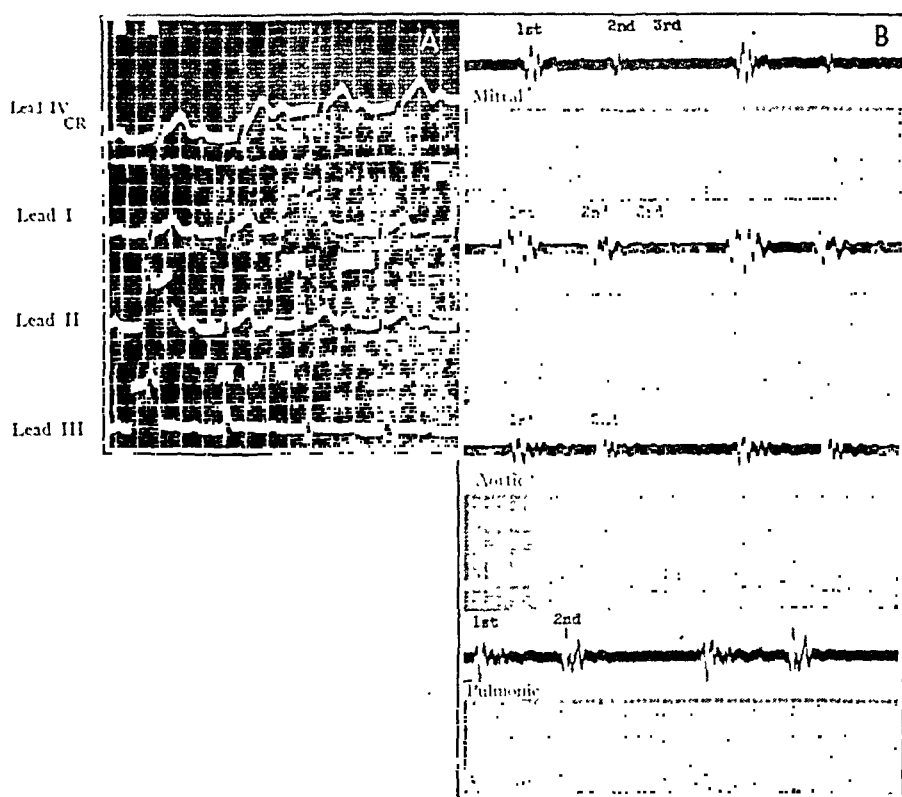


Fig. 1.—*A*, routine electrocardiogram taken on March 21, 1940. The only abnormality in the record is the prolonged PR interval measuring 0.36 second in lead IV. Lead IV<sub>CR</sub>, the routine fourth lead used in this study, was taken with the lead selector on lead I, employing the right arm electrode and cable on the right arm and the left arm cable and precordial electrode on the precordium. *B*, routine stethogram taken March 21, 1940. The sounds are all of normal contour and duration. A third heart sound is recorded on the tracings from the mitral and the tricuspid area. This sound is recorded at the latter area with greater clarity than it is at the former area.<sup>4</sup> A fine systolic vibration of low intensity is recorded at the mitral, the pulmonic and, intermittently, the aortic area. This vibration can be identified as the fine "saw tooth" ripple of the base line between the first and second sounds (compare figure 5).

diastolic, with a pulse rate of 60 per minute with the boy in the lying position. The apical impulse was felt 8.5 cm. from the midsternal line in the fifth intercostal space. No systolic or diastolic murmurs were heard. The heart sounds were normal.



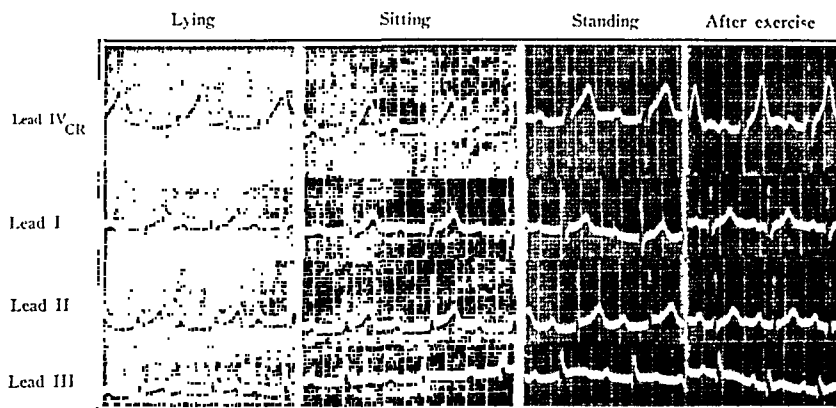


Fig. 2.—Electrocardiogram taken on May 27, 1940 to show the effect of various positions and exercise. As the subject passes from a resting to an active state voltage changes occur, an S wave appears in lead II and the ST segment in lead II is lowered. The PR intervals shorten from 0.36 second with the subject in the lying position to 0.34 second as he assumes the sitting position, then to 0.28 second as he stands erect and finally to 0.19 after he exercises.

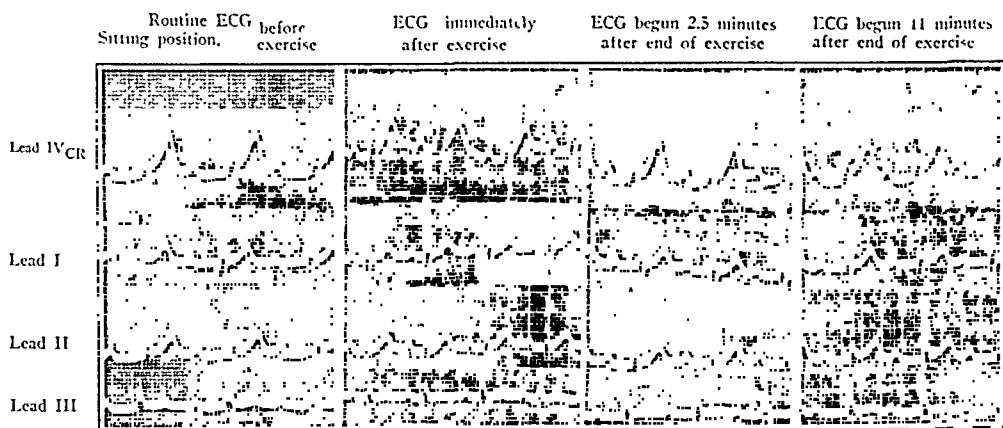


Fig. 3.—Electrocardiogram taken on Nov. 26, 1940, with the subject in the sitting position and the leads recorded in the following sequence: IV, I, II and III. The elapsed time between the beginning of one lead and the beginning of the sequential lead was 0.5 minute. Thus, for example, lead III of the series begun 11 minutes after the end of the exercise was actually recorded 12.5 minutes after the end of exercise.

The change in duration of the PR interval in lead IV is from 0.40 second before exercise to 0.18 second immediately after exercise. This is almost identical with the change recorded on May 27. The gradual elongation of the PR interval to its original value before exercise is shown in the tracings begun 2.5 minutes and 11 minutes after exercise. The PR interval in lead III, taken 12.5 minutes after exercise, had a duration of 0.34 second. This value, peculiarly, is greater than the 0.32 second for the PR interval in lead III recorded before exercise. Changes in the voltage of the S wave in lead II and the depression of the ST segment in lead II, which were brought on by exercise, are also seen to disappear 12 minutes after exercise.

*Laboratory Data.*—The Wassermann reaction of the blood was negative. Urinalysis, chemical studies of the blood and hematologic examination revealed nothing abnormal. Anterior-posterior and lateral roentgenograms and roentgen kymograms were taken before and after exercise. They revealed a heart of normal contour and dimensions.

*Electrocardiographic and Stethographic Examination.*—Method: The first electrocardiogram and stethogram were taken on March 21, 1940, with the boy in the sitting position (fig. 1 *A* and *B*).

The routine precordial lead ( $IV_{CR}$ ) was made with the precordial electrode and left arm cable on the precordium and the right arm electrode and cable on the right arm, with the lead selector on lead I. This method of taking lead  $IV_{CR}$  yields the same recording as is obtained by employing the method suggested by the American Heart Association. However, in comparison with the latter method, it has the distinct advantage of insuring greater speed and greater accuracy on the part of the technician.

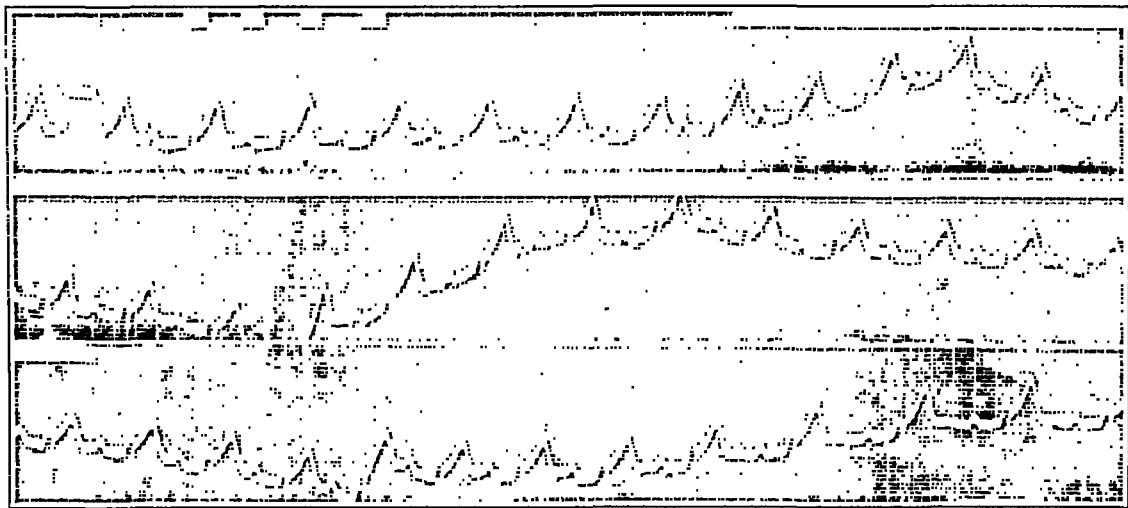


Fig. 4.—Electrocardiogram taken on Nov. 26, 1940 to show the effect of a deep, sustained inspiration on the PR interval. The three sections represent a continuous tracing. The four short white dashes at the beginning of the tracing (section 1) identify the lead employed ( $IV_{CR}$ ). The long white dash, beginning approximately 3 seconds later (section 1) and extending through to the beginning of the third section, marks the start, duration and end of a single deep inspiration. Measurements of the PR interval show that it varies from 0.31 to 0.34 second during normal respiration (the part of section 1 preceding the long white dash). For the duration of the sustained inspiration the PR interval varies from 0.26 to 0.30 second. In the third section, after the end of the dash and the resumption of normal respiration, the PR interval varies from 0.27 to 0.30 second.

The findings in the fourth lead are used throughout in describing the changes which form the basis of this report. This is done because no significant variation in the PR interval occurs in the different leads and the waves and complexes are recorded with greater clarity and amplitude in lead  $IV_{CR}$  than they are in the standard leads.

Heart sound tracings were taken at the mitral, tricuspid, aortic and pulmonic areas.<sup>3</sup> Respiration was suspended at the end of a normal expiration while the

3. A Sanborn Stetho Cardiette was employed throughout the study.

records were made. The mitral and tricuspid tracings in this case were both taken at the volume amplification of 4.2 on the instrument's arbitrary scale of volume setting; the aortic and pulmonic tracings were taken at the volume setting of 4.9. Lead II was run simultaneously with every sound recording.

**Electrocardiographic Findings:** The heart rate was recorded as 81.

The only abnormality noted in the record is a prolonged PR interval, measuring 0.36 second in lead IV. The variation in the PR interval of successive cycles in each lead was at no time greater than 0.02 second (fig. 1 *A*).

**Diagnosis:** The diagnosis was a marked degree of incomplete heart block.

**Stethographic Findings:** The vibrations of the heart sounds are of normal contour and duration at all areas (fig. 1 *B*). A perceptible systolic murmur is recorded at the mitral and the pulmonic area. (No murmur was heard by the physician who did the routine physical examination.)

A vibration of low frequency and low amplitude is visible after the second heart sound at the mitral and the tricuspid area. The position of this vibration in the diastolic phase suggests at first that it may be a third heart sound. However, this vibration shows a slightly more constant time relation to the P wave of the electrocardiogram than it does to the second heart sound of the stethogram. Furthermore, it is of greater amplitude at the tricuspid than at the mitral area (fig. 1 *B*). It is, therefore, more probable that this vibration represents a summation of the normal third heart sound and the auricular systolic rather than the third heart sound alone.<sup>4</sup>

**Special Observations.**—Because of the unusually long PR interval, the absence of dropped beats and the completely negative case history and physical examination, the boy was reexamined on May 27 and on November 26.

On May 27 electrocardiograms were made with the boy in the lying position after a rest period of 10 minutes; in the sitting and the standing position, and in the standing position after exercise. Figure 2 and the table show certain of the results obtained.

The outstanding features are tabulated as follows:

Position	Calculated Heart Rate, per Minute	Duration of PR <sub>IV</sub> , Second
Lying .....	75	0.35-0.38
Sitting .....	74	0.32-0.34
Standing .....	74	0.28-0.31
Standing After Exercise .....	90	0.18-0.19

4. Third heart sounds are infrequently observed. They are usually recordable at the mitral area only, rarely at the tricuspid area (Boone, B. R., and Ciocco, A.: *Cardiometric Studies on Children: I. Stethographic Patterns of Heart Sounds Observed in 1482 Children*, Milbank Mem. Fund Quart. **17**:323-357, 1939; *II. The Duration of the Component Parts of the Cardiac Sound Cycle*, *ibid.* **18**:137-155, 1940). When they are recorded at the latter area, the amplitude is always much lower. In this case the vibration in question on the tracing taken over the tricuspid area March 21, 1940 was recorded with an amplitude equal to, if not greater than, the amplitude of this vibration on the tracing taken over the mitral area (fig. 1 *B*). Furthermore, as has already been mentioned, there is some variation in the interval between this diastolic wave and the preceding second heart sound. The variation seems to depend on the occurrence of the P wave immediately preceding this diastolic vibration on the stethogram. It is therefore believed that the vibration represents a ventricular thud produced by the rush of blood into the ventricles during the period of rapid ventricular filling which is augmented by an auricular systole.

On November 26 electrocardiograms and stethograms were again taken (figs. 3 through 6 and table). The control electrocardiogram taken with the boy in the sitting position showed practically no variation, as compared with the preceding control graphs, except that the PR interval in lead IV was 0.38 to 0.40 second in duration. Immediately after exercise, this interval was 0.18 to 0.20 second. Two and a half minutes after the end of exercise the PR interval had increased to 0.26 to 0.28 second. After 11 minutes it showed a further increase to 0.31 second (fig. 3).

The effect of deep sustained inspiration on the PR interval was investigated, as shown by figure 4. A continuous tracing (lead IV<sub>CR</sub>) was taken before, during

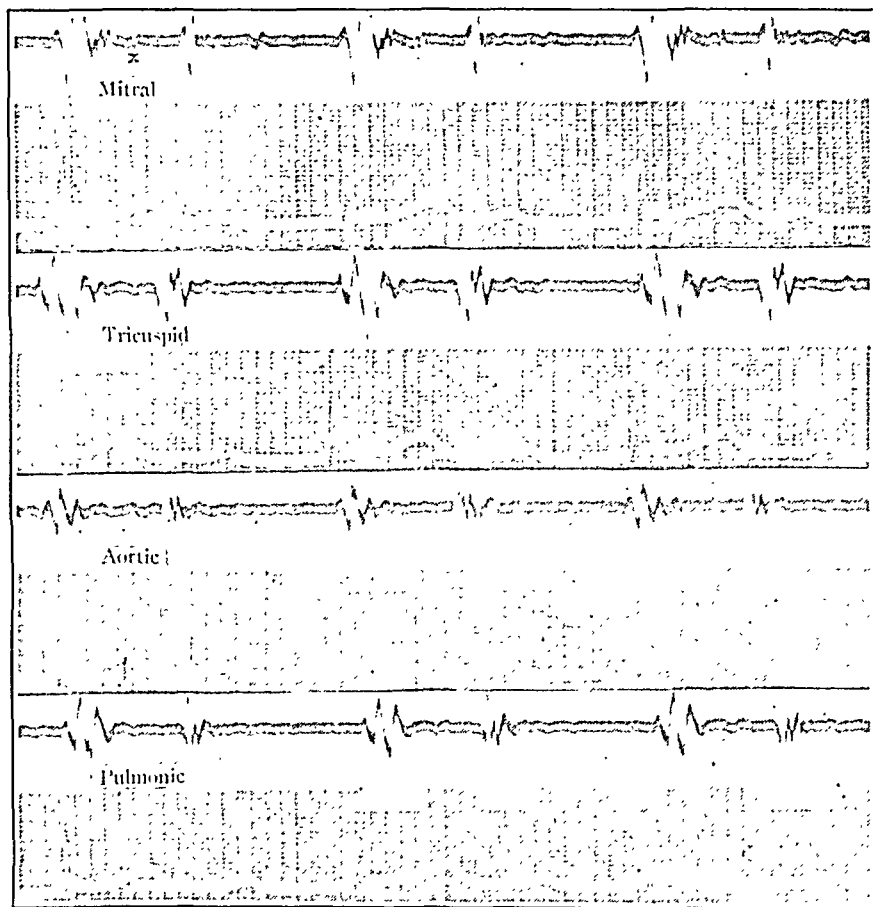


Fig. 5.—Stethogram taken on Nov. 26, 1940, showing an intermittent third heart sound recorded at the tricuspid area. The vibration appears clearly only in the last cycle of the record. (The vibration has a more constant character in figure 1 *B* in the tracing recorded at the tricuspid area.)

Further comparison of figure 5 with figure 1 *B* reveals the disappearance of the systolic vibrations previously recorded at the pulmonic zone. The systolic intervals of the pulmonic tracing in this figure are just as smooth as are the diastolic intervals. The series of fine systolic vibrations seen on the mitral tracing of figure 1 *B* are replaced in this figure by a single vibration (*x*) of low amplitude. Such vibrations are always visible in the electrocardiograms of persons who have an "intrasystolic click." Their significance here is uncertain. The variation was inaudible to the observer at the time the tracing was made.

and after a deep inspiration, which was held for 14 seconds. The PR interval during the 6 seconds preceding the beginning of the deep inspiration varies from 0.31 to 0.34 second (fig. 4—from the beginning of the tracing to the beginning of the white dash following the lead marks). During the deep breath (sustained from the PR interval preceding the white dash till the end of the dash) the PR interval varies from 0.26 to 0.30 second. Immediately after the end of inspiration and for the following 11 seconds the PR interval varies from 0.27 to 0.30 second.

It is therefore obvious that holding the breath after a deep inspiration had a slight but definite effect in shortening the PR interval. This observation is not in

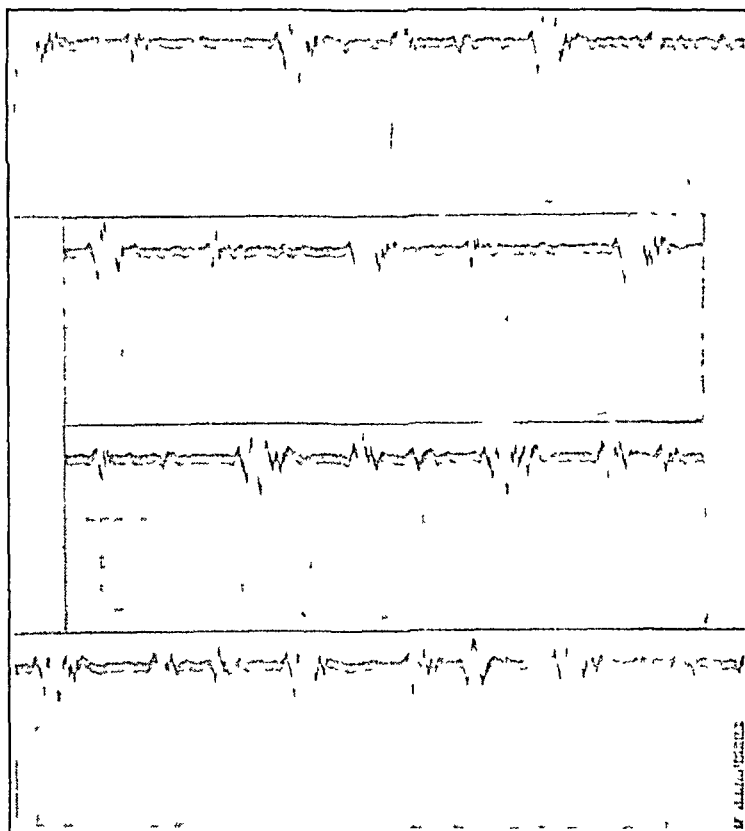


Fig. 6.—Stethogram taken on Nov. 26, 1940 to show the effect of respiration on the mid-diastolic vibration, or third heart sound. The four sections represent a continuous tracing. The subject suspended respiration for a few seconds after a normal expiration. Breathing was resumed during the diastole of the second heart cycle of section 1 (as shown by the disturbed base line). The third heart sound was inaudible throughout sections 1 and 2 and during part of section 3. It became audible in the last cycle of section 3 and reached its greatest intensity in section 4. The last cycle of section 4 shows the vibration reduced to its usual subaudible amplitude. This tracing was recorded at the mitral area.

agreement with that of Levy, who stated that in the subject whose case he reported a sustained inspiration induced the Wenckebach phenomenon, a condition equivalent to an increased auriculoventricular block.

*Comparison of Data in Four Cases of Incomplete Heart Block Due to Vagal Effect*

Author.....	Marzahn, <sup>1b</sup> case 1	Marzahn, <sup>1b</sup> case 2	Levy <sup>1a</sup>	Poel (case reported here)
Age.....	32 years	24 years	14 years	15 years
Complaints.....	Stitches and occasional pain in heart ever since an accident	Systolic mur- mur at apex; spastic consti- pation	Frequent faint- ing spells	None
Type of subject.....	Robust	Lean; athletic	Thin; under- nourished	Lean; well nour- ished; athletic
Clinical observation	Irregularity of heart beat	No abnormal- ities	Intermittence of pulse	No abnormalities
Roentgen examina- tion of heart	Normal	Normal	Bulging in region of pulmonary conus	Normal
Stethoscopic exami- nation of heart	Not given	Not given	Occasional occur- rence of a soft blowing systolic murmur at the pulmonic area	No murmurs
Condition of heart..	Organically sound	Organically sound	Organically sound	Organically sound
Control electrocardi- ogram	Rate = 70; partial 2:1 sino- auricular block; no conduction delay	Rate = 80; incomplete auriculoventricu- lar block; PR = 0.25 sec.	Rate = 86; second degree heart block; PR = 0.26 sec.	Rate = 81; incomplete auriculoventricu- lar block; PR = 0.36 sec.
Effect of holding a deep breath	Not given	Not given	Rate = 79; Wenckebach phenomenon occurred	Rate change insignificant; PR reduced from 0.33 to 0.28 sec.
Effect of exercise....	Rate = 120; PR = 0.12 sec.; regular sinus rhythm; no dropped beats	PR reduced to 0.20 sec.	Rate = 86; PR = 0.18 sec.; no dropped beats	Rate = 90; PR = 0.18 sec.
Effect of digitalis....	Not given	Not given	Increase of auriculoventricu- lar block	Not tried
Effect of atropine...	Rate = 108; disappearance of dropped beats	PR = 0.15 sec.; auriculoventricu- lar nodal rhythm induced	Auriculoventricu- lar block abolished	Not tried
Effect of position of patient on electro- cardiogram	Not given	Not given	Not given	PR longest in lying position (0.36 sec.), short- est in standing position (0.30 sec.)
Electrocardiographic variations exclusive of those induced by above means	Not given	Spontaneous variation of PR interval from 0.18 to 0.35 sec. from day to day	No variation noted	PR interval shortened to 0.18 sec. by exercise; gradual rever- sion to original duration after exercise
Stethographic exam- ination of heart	Not given	Not given	Not given	Inaudible auricu- lar (or third) heart sound re- corded at mitral area; sound markedly accen- tuated and audi- ble when beat- ing resumed after short periods of suspended respiration

An unusual variation in intensity and audibility of the diastolic vibration (or third heart sound) was heard stethoscopically at the time the effect of deep breathing was investigated. During normal respiration the vibration of this third heart sound could be observed visually by means of the stethographic galvanometer. It reached an audible intensity only occasionally, at which time it was heard as a soft, dull, thudlike sound. The control stethogram was taken with respiration suspended at the end of a normal expiration, during which time the diastolic vibration was inaudible. When respiration was resumed by the subject the intensity and audibility of this diastolic vibration showed a marked increase soon after the first inspiration. It reached an audible intensity, remained there for a number of cycles and then diminished to its usual level. A stethogram was taken to illustrate the phenomenon (fig. 6). The subject began to inhale after the second heart sound of the second cycle. The third heart sound became audible in the seventh cycle.

The table summarizes the comparable data in this case and in cases of similar disturbance recorded in the literature.

#### COMMENT

Since all clinical and laboratory findings appeared to show a normal cardiovascular system, the electrocardiographic data obtained were interpreted as indicative of a persistent auriculoventricular heart block due to vagal influence.

A review of the literature revealed that both auriculoventricular and sinoauricular heart block have been produced experimentally by stimulation of the vagus nerve. Robinson and Draper,<sup>2a</sup> in 1911, reported that stimulation of the right vagus nerve by pressure in a man with an anatomically normal heart had a more marked effect on the rate of the heart than had stimulation of the left vagus nerve. Stimulation of the latter seemed to have a more marked effect on the conduction of the cardiac stimulus from auricles to ventricles. Sigler<sup>2b</sup> reported the predominant vagal effects on the heart obtained on carotid sinus pressure to be sinoauricular slowing, or standstill, as well as various grades of auriculoventricular block. He found that pressure on the right carotid sinus had a greater tendency to produce complete standstill, whereas pressure on the left one had a greater tendency to produce complete auriculoventricular block. This he explained by stating that although terminal branches of both vagus nerves are present in each node, right vagal terminals are found in greater number in the sinus node, while left vagal terminals predominate in the auriculoventricular node. Wiggers'<sup>2c</sup> findings were in accord with those of Sigler. He stated that some vagal fibers from the right branch terminate in the sinoauricular node, decreasing its rate of discharge and consequently slowing the heart. He explained functional heart block produced by stimulation of the left

vagus nerve as due to those fibers from the left branch which connect with the auriculoventricular node and junctional tissue and act either by extending the refractory period or by decreasing the conductivity of the tissue in which they end. In this way heart block is produced which may range from slight delay of conduction to complete blockage of the impulse to the ventricle.

Thus, in the majority of cases vagal influence on the cardiac mechanism has been reported to result in (1) interference with the impulse formation in the sinoauricular node (when the right vagus nerve is stimulated), (2) interference with the conduction of the sinus impulse along the auriculoventricular junctional tissue and node (when the left vagus nerve is stimulated) or (3) varying degrees both of sinoauricular and of auriculoventricular nodal interference (if a generalized high vagal tone involving both vagus nerves is induced).

By viewing the case presented here and those previously reported in the light of the laboratory observations just mentioned, it would appear that the experimental data may be considered as a medium, or matrix, which brings together and provides a basis for relating the 4 cases summarized in the table. Conversely, it can be seen that these cases may represent instances of the spontaneous occurrence in apparently normal persons of conditions previously elicited only under experimental conditions.

Experimentally, the electrocardiographic abnormality seen in figure 1 *A* has been induced by other investigators, by stimulating the left vagus nerve. Thus, in the case presented here, in which there is no sign of sinoauricular nodal depression, no clinical or other abnormality is apparent and the only abnormal finding is a markedly prolonged PR interval, the origin may be explained by assuming that an activating agent producing a high vagal tone is present somewhere along the path of that branch of the vagus the fibers of which predominate in the region of the auriculoventricular node.

#### SUMMARY

A case of persistent functional heart block apparently due to vagal influence is presented. Three previously described cases of such disturbance are reviewed.

The frequency of occurrence of this phenomenon in normal adolescents is low. It was encountered only once in 2,400 electrocardiograms made on normal persons between the ages of 12 and 20.

Body position, body activity and respiration were found to have a definite effect on the duration of the PR interval in the case reported



here. Respiration also affected the intensity and audibility of a third heart sound, or auricular sound.

Observations pertaining to the effect on the heart of experimental excitation of the vagus nerve are reviewed. A possible explanation of the origin of functional heart block is suggested in the light of these observations.

Dr. C. E. Palmer, Division of Public Health Methods, National Institute of Health, and Dr. William Schmidt, medical director of the cooperative nutrition study, aided me in preparing this report and reviewed it before publication. Dr. Frank Liberson, radiologist, United States Public Health Service, made the roentgenograms, and Dr. Harry Gold, Cornell University Medical College, read the manuscript. Miss Carmeta Scott aided in preparing the manuscript.

# Progress in Internal Medicine

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## BLOOD

A REVIEW OF THE RECENT LITERATURE

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*(Concluded from p. 926)*

## INFECTIOUS MONONUCLEOSIS

Since the observation of Murray, Webb and Swann in 1926 that organisms of the genus *Listerella* (*Bacterium monocytogenes*) could produce mononucleosis in rabbits, there has been speculation as to their possible etiologic relation to infectious mononucleosis in human beings. The evidence as to the importance of this organism in relation to the disease is conflicting. This is because in only a small proportion of cases can it be cultivated from the blood and the spinal fluid and because it has not been demonstrated that antibodies against organisms of this group develop in the serum of patients with infectious mononucleosis. Janeway and Dammin<sup>209</sup> undertook a study to ascertain whether in patients with infectious mononucleosis agglutinins develop for either of the two known serologic groups of the genus *Listerella*. They observed that in all but 3 members of the normal control group the results of the sheep cell agglutination test fell within the normal range given by most authors, namely, agglutination in a final dilution of 1:64 or less. These 3 exceptions occurred in the serum of patients who had received horse serum for the treatment of pneumonia, and the highest titer, 1:1,024, was recorded in a patient with serum disease. The authors emphasize that it has been known for some time that the injection of horse serum will lead to the production of "heterophile" antibodies. The results of the *Listerella* agglutination tests showed a slightly elevated

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209. Janeway, C. A., and Dammin, G. J.: Studies on Infectious Mononucleosis: The Relationship of the Organism of the Genus *Listerella* to the Disease, as Studied by the Agglutination Reaction, *J. Clin. Investigation* **20**:233, 1941.

titer in the serum of the patients with infectious mononucleosis as compared to that in the serum of the control groups, but there was no significant trend upward or downward in the *Listerella* agglutinin titer during the course of the disease or recovery from it. From these observations it was concluded that the study did not suggest any definite etiologic relation between the known *Listerella* organisms and infectious mononucleosis.

Sundberg <sup>210</sup> presents one of the most complete general articles dealing with infectious mononucleosis that has been published recently, and excellent photomicrographs of the infectious mononucleosis type of cell are reproduced. The author believes that blood studies afford the best basis for a diagnosis of the disorder, since the clinical manifestations may be varied and may simulate those of other conditions. In her opinion, the heterophile antibody test, which usually gives a positive reaction in the presence of the disease, is of great value, but it is not absolutely necessary for the diagnosis. The serious nature of some of the diseases with which infectious mononucleosis may be confused is emphasized, and for this reason the importance of an accurate diagnosis is stressed.

Barber <sup>211</sup> considers that infectious mononucleosis is probably a virus disease, fairly common in occurrence and of well recognized epidemiologic character. In 3 of his patients with the disease the outstanding feature was ulceration of the tonsils which was remarkably resistant to all forms of therapy.

It is emphasized by Werlin, Dolgopol and Stern <sup>212</sup> that infectious mononucleosis is of relatively frequent occurrence but that the disease is often not recognized. It may be confused with diphtheria, epidemic parotitis (mumps), follicular tonsillitis, streptococcic pharyngitis, sinusitis and various other infections. A general description of the syndrome is given. The authors state that the highest leukocyte count is observed during the first week of illness in children and during the second week of illness in adults. The heterophile antibody reaction was positive in 90 per cent of their series of cases. According to their experience, the titer of serum showing a positive heterophile antibody reaction remains constant for months if the serum is stored in an ice box. The suggestion is made that serum giving a positive reaction be used as a control in performing the test with serum the reaction of which is unknown.

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210. Sundberg, D.: Infectious Mononucleosis, Detroit M. News, Educ. Issue **32**:29, 1941.

211. Barber, H. S.: Anginose Glandular Fever, *Lancet*, **1**:71, 1941.

212. Werlin, S. J.; Dolgopol, V. B., and Stern, M. E.: Infectious Mononucleosis—Diagnostic Problem, *Am. J. M. Sc.* **201**:474, 1941.

Mayer<sup>213</sup> presents a general article dealing with all aspects of the syndrome of acute infectious mononucleosis. A description of the clinical picture of infectious mononucleosis with special reference to cerebral complications is given by Thelander and Shaw.<sup>214</sup> They present a comprehensive résumé of present knowledge of all aspects of the disease. It is stressed that headache is the symptom referable to the nervous system which is common to all patients. Other manifestations are variable. There may be evidence of encephalitis with difficulty in speech, sluggishness and some mental confusion. Ptosis may be present. Evidence of meningitis with stiffness of the neck is, however, the most common sign of involvement of the nervous system. There is usually a moderate increase in the number of cells in the spinal fluid, averaging 50 to 80 per cubic millimeter, but the number may be as great as 600 or more. The exact pathologic changes in the nervous system are still obscure, but it appears from the authors' observations that there may be involvement of the brain or of the meninges or possibly of both. To date there has been no record of late sequelae. A case of infectious mononucleosis in which the manifestations in the nervous system were outstanding is reported by Landes, Reich and Perlow.<sup>215</sup> They emphasize that involvement of the nervous system is regarded as rare in this disease, but this is not entirely correct, as undoubtedly the true diagnosis is overlooked in some instances. This occurs especially in patients in whom the symptoms referable to the nervous system are recognized for as long as two weeks prior to the appearance of the lymphadenopathy. Usually headache and evidences of meningeal irritation, such as positive Kernig and Brudzinski signs, nausea and vomiting, are present. It is stated that characteristically the symptoms and signs referable to the nervous system disappear, with no residuum. The changes in the spinal fluid are neither diagnostic nor constant. The pressure may be elevated, and pleocytosis is variable, usually with a cell count of 25 to 300, largely lymphocytes. The total protein may be increased, as well as the globulin fraction. The Wassermann reaction and the colloidal gold curve of the spinal fluid are negative. Apparently, observations on the heterophile antibody reaction of the spinal fluid have not been previously reported; in this case the reaction was negative. The presenting clinical picture in this case was acute ataxia with an outspoken involvement of the

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213. Mayer, O. B.: Acute Infectious Mononucleosis, *J. South Carolina M. A.* **37**:48, 1941.

214. Thelander, H. E., and Shaw, E. B.: Infectious Mononucleosis with Special Reference to Cerebral Complications, *Am. J. Dis. Child.* **61**:1131 (June) 1941.

215. Landes, R.; Reich, J. P., and Perlow, S.: Central Nervous System Manifestations of Infectious Mononucleosis: Report of a Case, *J. A. M. A.* **116**:2482 (May 31) 1941.

cerebellar system. In the opinion of the authors, the pathologic process, regardless of whether it should be regarded as encephalitis or toxic encephalopathy, extended over a considerable portion of the brain. As the lymphadenopathy and splenomegaly did not appear until twenty-two days after the onset of the symptoms, the diagnosis would probably have been missed except for the positive heterophile antibody reaction (1:2,048). They emphasize that this test should be employed in all cases in which there are acute and obscure cerebral symptoms.

According to Smith,<sup>216</sup> two types of conditions are encountered in young patients which are characterized by lymphocytosis and are consequently frequently confused with infectious mononucleosis or even with leukemia. In one type there is a transient, unexpected hyperleukocytosis with an absolute and a relative increase in lymphocytes which is unassociated with recognizable symptoms or physical signs. The second type, which is more frequently encountered, follows infections of the upper respiratory tract of varying intensity. It is characterized by fever of low grade, present for weeks or months, and associated symptoms, which frequently include anorexia, pallor, fatigability and paraumbilical pain. In both conditions there is a preponderance of lymphocytes in the blood with a normal or a moderate elevation of the cell count. These two syndromes are classified as acute and chronic infectious lymphocytosis and are differentiated clinically, hematologically and serologically from infectious mononucleosis, leukemia and miscellaneous infections commonly associated with lymphocytosis. The heterophile antibody reaction in patients with either condition is negative, and the bone marrow shows only an increase in the lymphocytes. Two cases of the first type, which the author designates as acute infectious lymphocytosis, were encountered in children 3½ and 6 years of age. The leukocyte counts were 92,000 and 44,300 per cubic millimeter and the lymphocyte percentages reached 86 and 79, respectively. The course of illness in each child was benign, and in neither was there lymphadenopathy, enlargement of the spleen or the clinical or physical signs characteristic either of infectious mononucleosis or of leukemia. The results of examination of sternal marrow ruled out leukemia, and the blood picture could be readily differentiated from that of infectious mononucleosis or leukemia. In neither instance did the heterophile antibody test give a positive result. (We call attention to an article by Reyersbach and Lenert, abstracted in this section, in which an apparently similar syndrome was regarded as infectious mononucleosis.) The second type occurs most commonly in infants and in young children and is frequently encountered in pediatric practice. This group includes cases in which

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216. Smith, C. H.: Infectious Lymphocytosis, *Am. J. Dis. Child.* **62**:231 (Aug.) 1941.

after an infection of the upper respiratory tract a low grade fever continues to be present for prolonged intervals. Associated symptoms are those usually observed in any mild chronic infection. The blood in such cases shows moderate leukocytosis with an increased lymphocytic percentage instead of the anticipated neutrophilic response. The total leukocyte count in these cases varies from slightly above normal to 18,000 or 20,000 per cubic millimeter, and the lymphocytes are commonly found to comprise 70 to 80 per cent of the white cells. In neither type of the disease is there a significant decrease in the number of red cells or in the hemoglobin content. The author considers that acute and chronic infectious lymphocytosis may represent separate entities, although there is some evidence that they may be related. It is his belief that the etiologic agent of each type is probably an undetermined virus which is related to infection of the upper respiratory tract.

An important study is reported by Reyersbach and Lenert,<sup>217</sup> who observed 16 cases of what was regarded as atypical infectious mononucleosis in a group of 108 children who were receiving convalescent care for rheumatic fever. According to the authors, the outbreak of the disease differed from any other hitherto reported in that none of the children had symptoms or physical signs of any kind. The condition was discovered accidentally because examination of the blood was done at regular intervals as part of the general medical care. The maximum leukocyte counts of the 16 children varied from 18,400 to 59,300 cells per cubic millimeter, and the proportion of lymphocytes rose to a maximum of 93 per cent and was never lower than 71 per cent at the height of the disease. The predominating cell was of the normal small lymphocytic type. The large lymphocytes typical of infectious mononucleosis were not present. The heterophile antibody test in each instance gave a negative reaction, as did the Wassermann test which was done in 5 cases. The condition may be regarded as acute infectious lymphocytosis of the type reported by Smith and discussed in the preceding paragraph.

Fuller<sup>218</sup> reports 5 cases in which the patients had all of the more important clinical features of infectious mononucleosis except that the heterophile antibody reaction was positive in such a low titer (below 1:80) in 4 cases that it was not considered diagnostic. The test was not done in 1 case. The author concludes that if a positive heterophile antibody reaction is essential for the diagnosis of infectious mononucleosis, some other unknown factor appears to be capable of producing mononucleosis with a secondary infection of the throat and a generalized

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217. Reyersbach, G., and Lenert, T. F.: Infectious Mononucleosis Without Clinical Signs or Symptoms, *Am. J. Dis. Child.* **61**:237 (Feb.) 1941.

218. Fuller, C. J.: Angina of the Throat Associated with Mononucleosis, *Lancet* **1**:69, 1941.

hyperplasia of the lymphoid tissues. The differential diagnosis of the condition reported and acute leukemia, agranulocytosis and diphtheria is discussed.

Warren <sup>219</sup> considers that the changes in the white cells and the serologic reactions are the two characteristic manifestations which differentiate the entity of infectious mononucleosis from other disorders presenting a similar clinical picture. The author has investigated the question of why the typical abnormal white cells of infectious mononucleosis may be present without an elevated heterophile titer. It is concluded that the Forssman heterophile antibodies are probably increased prior to the development of the antibodies of this disease and possibly are essential to their appearance. The typical lymphocytes of infectious mononucleosis are frequently found in disease conditions in which a positive Paul-Bunnell reaction has not been obtained. Only when these cells are present in considerable numbers does the elevated heterophile titer develop.

Barrett <sup>220</sup> believes that the lack of agreement concerning the percentage of cases of infectious mononucleosis in which sheep cell agglutination occurs is due, among other possible causes, to the unwitting use by different workers of various standards in the performance of the test. From his studies it is concluded that sheep cell titers of 1:80 and horse cell titers exceeding 1:320 should be regarded as positive. No advantage is claimed in using horse cells instead of sheep cells. The value of absorption tests was discussed and a new technic described, which the author believes has practical advantages over other methods, although it does not embody any important new principles. Of over 300 samples of normal serum examined by this method, 5 contained small amounts of an antibody indistinguishable from that found in the serum of patients with infectious mononucleosis and 10 others contained a sheep cell agglutinin probably different from any yet recognized in human serum.

Kaufman <sup>221</sup> presents a careful review of the literature and his own observations on the occurrence of false positive serologic reactions for syphilis in patients with infectious mononucleosis. He considers that the actual incidence of recognized false positive reactions in patients with this disease would seem to be between 2 and 10 per cent. It is advised by the author that when a Wassermann reaction is encountered which is suspected of being falsely positive, a heterophile antibody test should

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219. Warren, E. W.: Observations on Infectious Mononucleosis, *Am. J. M. Sc.* **261**:483, 1941.

220. Barrett, A. M.: The Serological Diagnosis of Glandular Fever (Infectious Mononucleosis): A New Technique, *J. Hyg.* **41**:330, 1941.

221. Kaufman, R. E.: False Positive Serologic Reactions for Syphilis in Infectious Mononucleosis, *J. Lab. & Clin Med.* **26**:1439, 1941.

be performed. The cause of the false positive reactions in patients with infectious mononucleosis is unknown. Eagle considers that they may be due to the effect of some native amboceptor (antibody for sheep red cells) on the Wassermann reaction. The possibility that this may account for the false positive flocculation tests (Kline, Kahn, Eagle, Meinicke, etc.) is clearly excluded, since red cells are not employed in this type of reaction. The suggestion is made by Kaufman that patients should not be treated for syphilis until serologic reactions suspected of being falsely positive have had a sufficient opportunity to revert to negative.

Mohr, Moore and Eagle<sup>222</sup> call attention to the fact that infectious mononucleosis has been reported repeatedly as a cause for biologic false positive tests for syphilis. In a review of the literature they found that the various serologic tests for syphilis are observed to yield positive reactions in 18 to 50 per cent of cases of infectious mononucleosis. Bernstein is cited as stating that the false positive reaction is transitory, rarely occurs over a longer period than three months and generally reverts to negative before the end of the third week of the disease. According to the authors, the nonspecificity of the tests for syphilis extends to the complement fixation (Wassermann) and the flocculation (Kahn, Kline, Eagle, Hinton and Laughlen) tests. Not included in this statement, however, is the complement fixation test with a spirochetal antigen (the so-called "pallida" test). It is possible that this procedure, like the Kahn verification test, may prove useful in the differentiation of positive serologic reactions due to syphilis and those due to other causes.

King<sup>223</sup> reports the case of a 23 year old consulting engineer who had experienced the symptoms of infectious mononucleosis for two and a half weeks. On the morning of entry into the hospital, he got out of bed to go to the toilet and was seized with a sudden agonizing pain in the abdomen which radiated through to the back. Laparotomy was performed promptly, and the spleen was seen to be ruptured and draining blood freely. Splenectomy was done, and recovery was uneventful. The patient's blood showed the characteristic changes of infectious mononucleosis; the heterophile antibody reaction was positive in a dilution of 1:1,256, and the symptoms prior to the acute abdominal episode were clear indications that the patient was suffering from this disease when the spontaneous splenic rupture occurred. The spleen weighed 660 Gm. and presented a microscopic picture which was

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222. Mohr, C. F.; Moore, J. E., and Eagle, H.: Biologic False Positive Serologic Reactions in Tests for Syphilis: II. Occurrence with Organic Diseases Other Than Syphilis, *Arch. Int. Med.* **68**:1161 (Dec.) 1941.

223. King, R. B.: Spontaneous Rupture of the Spleen in Infectious Mononucleosis: Report of a Case, *New England J. Med.* **224**:1058, 1941.



reported as compatible with infectious mononucleosis. Aside from a possibly similar occurrence which was recorded in 1932, the literature contains no report suggesting rupture of the spleen in this condition. It is of interest to record that we observed a case in the autumn of 1941 in which it was highly probable that the spleen ruptured after slight trauma in a patient with infectious mononucleosis.

Philip <sup>224</sup> reports the case of a man aged 21 who had fever and pain in the abdomen of five days' duration. Physical examination was of no assistance in disclosing the cause of the patient's symptoms. The blood, however, showed 58 per cent lymphocytes on the initial examination, and later they increased to 66 per cent. This led to a heterophile antibody test, which was reported as yielding a positive reaction in a dilution of 1:256. It was established, therefore, that the patient had infectious mononucleosis and was 1 of the group of almost 20 per cent of the patients with this disease whose chief complaint is abdominal pain. The author suggests that all patients with unexplained fever, especially in the presence of lymphocytosis, should have a heterophile antibody test done despite the absence of lymphadenopathy or splenomegaly.

Martin <sup>225</sup> emphasizes the diagnostic difficulty which may be experienced when jaundice appears in a patient with infectious mononucleosis before lymph glands become enlarged. Under such circumstances, the diagnoses which are likely to be considered are catarrhal jaundice and cholecystitis. The possibility arises that an erroneous diagnosis of the preeruptive stage of syphilis may be made, as the Wassermann reaction may also be positive for patients with infectious mononucleosis. The author reports 2 cases of jaundice associated with infectious mononucleosis. In 1 case the jaundice was prominent and preceded the usual glandular enlargement, while in the other it occurred as a transient feature during the course of an otherwise typical attack of infectious mononucleosis. Martin believes that the jaundice is of the obstructive type and probably arises from enlargement of glands in the hilus of the liver.

Sadusk <sup>226</sup> has considered the importance of the cutaneous eruption and the false positive Wassermann reaction which sometimes occur in cases of infectious mononucleosis. According to him, the changes in the skin may resemble those characteristic of German measles, typhoid fever, syphilis, scarlet fever, serum disease or even typhus fever. The

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224. Philip, A. J.: Infectious Mononucleosis: Unusual Case, *New York State J. Med.* **41**:1664, 1941.

225. Martin, L.: Glandular Fever with Jaundice: Report of Two Cases, *Lancet* **2**:480, 1941.

226. Sadusk, J. F., Jr.: The Skin Eruption and False Positive Wassermann in Infectious Mononucleosis (Glandular Fever), *Internat. Clin.* **1**:239, 1941.

occurrence of the cutaneous manifestations of the disease and the false positive Wassermann reaction, either singly or together, has been noted previously, but the association is perhaps not well known. A comprehensive review of the literature relating to the cutaneous manifestations of infectious mononucleosis and the false positive Wassermann reaction is given. The author observes that the rash appears most frequently from the fourth to the tenth day of the disease, although it may be as early as the third and as late as the twentieth day. It usually involves the trunk and the upper portion of the arms and occasionally the face and forearms. Itching is mild or absent, and the rash fades in two to seven days without desquamation except in rare instances after the erythematous type. It is usually stated that the rash is present in 17 to 19 per cent of cases, but in the author's experience it has occurred in only 7 per cent, which is more in accord with Bernstein's figure of 9 per cent. The exanthem is macular or maculopapular, although erythematous, urticarial, petechial, purpuric and vesicular types have been described. It has been known since 1928 that a temporarily positive Wassermann reaction may occur during the course of infectious mononucleosis. According to the literature reviewed, this is probably present in 8 to 16 per cent of cases, depending on the frequency with which the blood is tested. The false positive reaction ordinarily appears during the second week of the disease and usually reverts to negative within two weeks, although occasionally it may persist for over two months and even as long as three months. The false reaction affects the result of the Kahn test (or other types of flocculation procedures) as well as the Wassermann reaction. The nature of any of the immunologic reactions in cases of infectious mononucleosis has not been adequately explained, although several suggestions relating to the cause are made by the author.

Thomsen<sup>227</sup> describes 3 cases of infectious mononucleosis in which combined treatment with sulfanilamide and convalescent serum was employed. The results were gratifying, as evidenced by a rapid return of the body temperature to normal and a disappearance of all symptoms. In comparing 31 cases in which treatment was with sulfanilamide alone with a control group in which no special form of therapy was used, the author concluded that apparently the treatment may shorten the course of the disease somewhat but not sufficiently to justify definite conclusions. According to him, sulfanilamide may exert its beneficial effects on the secondary invading organisms which are responsible for some of the pathologic changes in the mouth and throat rather than on the primary cause of the disease.

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227. Thomsen, S.: Effect of Sulfanilamide on Infectious Mononucleosis, *Ugesk. f. læger* **102**:779, 1940.

## LYMPHOMATOID DISEASES, LEUKEMIA AND RELATED DISORDERS

*Hodgkin's Disease.*—In his analysis of 212 cases of Hodgkin's disease Goldman<sup>228</sup> noted that the disease exacts its toll from all races and afflicts males twice as frequently as females. The incidence was greatest in the third decade of life, although in his series of cases the ages ranged from 6 to 76 years. The initial symptom presented in 79 per cent of the cases was glandular enlargement, whereas in only 8 per cent the patients complained primarily of cachectic symptoms. Unilateral glandular enlargement usually developed first, a differential diagnostic point in Hodgkin's disease, since in leukemia and lymphosarcoma lymphadenopathy is most frequently bilateral. Splenomegaly commonly occurred late in the course of Hodgkin's disease. The skin was involved in 38 per cent of cases, the lesions consisting of exfoliative dermatitis or multiple nodules, with pruritus as an outstanding symptom. In 7 per cent skeletal lesions occurred, which resembled metastatic carcinoma in roentgenologic appearance. In 5 per cent of the cases definite involvement of the nervous system was present, with the spinal cord most commonly affected. The average length of life after the onset of symptoms was thirty-two months. In his analysis of the blood picture the author found that neutrophilia, relative monocytosis and lymphocytopenia were most characteristic, while eosinophilia occurred in only 20 per cent of the cases.

In their analysis of 65 cases of Hodgkin's disease in British patients Baker and Mann<sup>229</sup> found no definite etiologic relation between tuberculosis and Hodgkin's disease and noted no characteristic blood picture. In their patients fever was usually associated with visceral or deep glandular involvement, while the average length of survival after the onset of symptoms was eighteen months. Surgical eradication of involved superficial glands followed by irradiation therapy is advocated if the disease is well localized in an easily accessible region. Otherwise, roentgen therapy must be employed as a palliative measure. Although admitting that surgical intervention has benefited some patients with Hodgkin's disease, O'Brien<sup>230</sup> feels that roentgen rays are still the therapeutic mainstay. He presents a detailed description of his irradiation technic. Sayago<sup>231</sup> notes that radium applied externally to the chest may cause marked shrinkage of deep intrathoracic nodes.

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228. Goldman, L. B.: Hodgkin's Disease: Analysis of Two Hundred and Twelve Cases, J. A. M. A. **114**:1611 (April 27) 1940.

229. Baker, C., and Mann, W. N.: Hodgkin's Disease, Lancet **1**:23, 1940.

230. O'Brien, F. W.: End Results in Irradiated Hodgkin's Disease, Am. J. Roentgenol. **46**:80, 1941.

231. Sayago, C.: Radium Therapy in Hodgkin's Disease, Am. J. Roentgenol. **42**:888, 1939.

Of 54 cases of Hodgkin's granuloma studied by Burger and Lehman,<sup>232</sup> 3 were investigated for the possibility of concurrent brucella infection. In 1 case a culture of the blood was positive for *Brucella*. They believe the life expectancy of treated patients with Hodgkin's granuloma is three times that of untreated patients. Forbus and Gunter<sup>233</sup> have studied the pathogenicity of strains of *Brucella* isolated from 5 patients who died of typical Hodgkin's disease. They found that suspensions of tissues from these patients injected into guinea pigs failed to produce typical lesions of brucellosis but that the pure cultures of *Brucella melitensis* and *Brucella suis* isolated from these tissues did result in a mild form of the disease when administered intraperitoneally to guinea pigs. Poston and Parsons<sup>234</sup> present their method for the culture of *Brucella* organisms from lymph nodes.

Acuña and Bonduel<sup>235</sup> report the case of a child with Hodgkin's disease complicated by Mikulicz's syndrome. From a biopsy specimen of a lymph node they isolated a strain of streptococcus to which they attributed etiologic significance, stating that an uncontrolled infection may cause the reticuloendothelial system to react in a pathologic manner producing Hodgkin's disease.

Thoracic lesions are commonly encountered in Hodgkin's disease, according to Vieta and Craver,<sup>236</sup> who diagnosed such lesions in 74 per cent of 335 cases. They believe Hodgkin's disease does not produce a pathognomonic roentgen appearance. Charr and Wascolomis<sup>237</sup> report a case in which hemoptysis was the presenting symptom. At autopsy the right main bronchus was found obstructed by a large polypoid mass of Hodgkin's granuloma. There was also a pleural effusion. The condition of a 15 year old boy was diagnosed by bronchoscopy, according to Hammond,<sup>238</sup> who obtained material for biopsy from a mediastinal mass which had perforated the trachea. Garvin<sup>239</sup> reports the first

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232. Burger, R. E., and Lehman, E. P.: Hodgkin's Disease: Review of Fifty-Four Cases, *Arch. Surg.* **43**:839 (Nov.) 1941.

233. Forbus, W. D., and Gunter, J. U.: Pathogenicity of Strains of *Brucella* Obtained from Cases of Hodgkin's Disease, *South. M. J.* **34**:376, 1941.

234. Poston, M. A., and Parsons, P. B.: Isolation of *Brucella* from Lymph Nodes, *J. Infect. Dis.* **66**:86, 1940.

235. Acuña, M., and Bonduel, A.: Linfogranulomatosis maligna y síndrome de Mikulicz, *Arch. argent. de pediat.* **15**:128, 1941.

236. Vieta, J. O., and Craver, L. F.: Intrathoracic Manifestations of Lymphomatoid Diseases, *Radiology* **37**:138, 1941.

237. Charr, R., and Wascolomis, A.: Pulmonary Lesions in Hodgkin's Disease, *J. A. M. A.* **116**:2013 (May 3) 1941.

238. Hammond, A. E.: Perforation of the Trachea by Mediastinal Tumor (Hodgkin's Disease), *Ann. Otol., Rhin. & Laryng.* **50**:929, 1941.

239. Garvin, C. F.: Hodgkin's Diseases of the Heart and Pericardium, *J. A. M. A.* **117**:1876 (Nov. 29) 1941.

antemortem diagnosis of Hodgkin's disease of the heart and pericardium. By cystoscopy Phillips<sup>240</sup> noted gray-yellow nodules in the bladder of a patient with known Hodgkin's disease in whom dysuria, pyuria and hematuria improved considerably after radiation therapy.

In 2 cases presented by Winkelman and Moore<sup>241</sup> the patients showed evidence of marked lesions of the nervous system. One patient had granulomatous plaques on the dura mater overlying the brain, with associated cerebral softening, and involvement of the spinal cord and the brachial plexus. The other had a commoner type of epidural granuloma compressing the thoracic cord, with resultant symptoms of transverse myelitis. Meyer<sup>242</sup> describes marked improvement following roentgen ray therapy in a case in which vertebral and spinal cord damage was extensive. Lisa<sup>243</sup> reports a case of Hodgkin's disease complicated by herpes zoster and Raynaud's disease.

An interesting type of cutaneous granuloma has been described by Kierland and Montgomery.<sup>244</sup> Erythematous plaques which soon deteriorated into ulcerated areas developed on the chest of an 18 year old youth. Biopsy of nonulcerated plaques revealed histologic changes which were typical of Hodgkin's granuloma.

That the life span may not necessarily be short after the development of symptoms of this dread disease is illustrated by the case reported by Nolan,<sup>245</sup> in which the duration was eight and a half years, and 1 reported by Finkelstein,<sup>246</sup> in which the patient survived fourteen years.

Clinicians have long been interested in the effect of pregnancy on the course of Hodgkin's disease. Kushner<sup>247</sup> and Meyer<sup>242</sup> report that no ill consequences were noted after pregnancies in their patients. The children were apparently normal.

From his experience Steiner<sup>248</sup> concludes that the generally discredited Gordon test is of some value in cases in which the diagnosis of

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240. Phillips, R.: Hodgkin's Disease in the Bladder, *Lancet* **1**:480, 1941.

241. Winkelman, N. W., and Moore, M. T.: Hodgkin's Disease of Central Nervous System: Clinico-Pathological Study, *J. Nerv. & Ment. Dis.* **93**:82, 1941.

242. Meyer, O. O.: Some Therapeutic Experiences with Hodgkin's Disease, *J. A. M. A.* **117**:595 (Aug. 23) 1941.

243. Lisa, J. R.: Neurologic Complications in Hodgkin's Disease, *New York State J. Med.* **40**:62, 1940.

244. Kierland, R. R., and Montgomery, H.: Cutaneous Ulcerative Hodgkin's Disease, *Proc. Staff Meet., Mayo Clin.* **16**:124, 1941.

245. Nolan: Two Cases of Hodgkin's Disease, *New Zealand M. J.* **40**:306, 1941.

246. Finkelstein, W.: Unusual Case of Hodgkin's Disease, *Connecticut M. J.* **5**:687, 1941.

247. Kushner, J. I.: Pregnancy Complicating Hodgkin's Disease (Lymphogranuloma Malignum), *Am. J. Obst. & Gynec.* **42**:536, 1941.

248. Steiner, P. E.: Reliability and Significance of the Gordon Test in Hodgkin's Disease, *Arch. Path.* **31**:1 (Jan.) 1941.

Hodgkin's disease cannot be made with certainty from pathologic specimens, although he concurs in the opinion of other recent investigators that the reaction is nonspecific. Of 229 cases of Hodgkin's disease, the reaction was positive in 74 per cent, while in only 2 per cent of 452 control cases were positive results obtained.

Charache <sup>249</sup> reports the presence of Hodgkin's disease in 1 member of a set of homologous twins. The other twin was completely normal.

*Lymphosarcoma*.—Davis <sup>250</sup> classifies lymphosarcoma of the tonsil into three clinical types. The commonest is that in which one tonsil enlarges rapidly, with involvement of cervical lymph nodes. The tonsil is soft, friable and bleeds easily, and the capsule is absent. The second type is termed anginoid, in which a deep ulcer occurs in the tonsillar region. Lymphadenopathy is usually slight. In the third class there are marked regional lymph node metastases without a prominent primary site. The usual duration of life after the onset of symptoms in any of the three types is less than eighteen months. Wax <sup>251</sup> reports a case in which diagnosis was made by routine pathologic section and emphasizes the importance of such microscopic examination. Garcia Lopez <sup>252</sup> reports a tonsillar lymphosarcoma in a 3 year old boy. The author believes this to be the lowest age recorded for the occurrence of this type of neoplasm. In the case reported by Freedman <sup>253</sup> the hard palate was the primary site, a rare locality for this kind of tumor.

Potzky and Freid <sup>254</sup> state that nasopharyngeal lymphosarcoma rarely erodes the base of the skull to produce a basilar brain syndrome. Nasopharyngeal carcinoma, on the other hand, frequently causes this syndrome. The authors feel that nasopharyngeal lymphosarcoma may be cured by irradiation. They report a case in which skull erosion and symptoms and signs referable to the nervous system did not respond to therapy. At necropsy the bony destruction was found to be due to osteomyelitis rather than to tumor invasion.

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249. Charache, H.: Tumors in One of Homologous Twins: Hodgkin's Disease; Osteogenic Sarcoma, *Am. J. Roentgenol.* **46**:69, 1941.

250. Davis, E. D. D.: Clinical Aspects of Lymphosarcoma of the Tonsil, *Proc. Roy. Soc. Med.* **34**:679, 1941.

251. Wax, W. V.: Primary Lymphosarcoma of the Tonsil: Importance of Sending Removed Tonsils to the Laboratory for Pathological Diagnosis, *New York State J. Med.* **39**:2284, 1939.

252. Garcia Lopez, A.: Linfosarcoma de la amígdala en un niño de 3 años de edad, *Bol. Soc. cubana de pediat.* **13**:343, 1941.

253. Freedman, L. J.: Primary Lymphosarcoma of the Hard Palate, *Am. J. Roentgenol.* **43**:702, 1940.

254. Potzky, H., and Freid, J. R.: Osteomyelitis of Occipital Bone Complicating Roentgen Treatment of a Nasopharyngeal Lymphosarcoma, *Am. J. Roentgenol.* **43**:584, 1940.

Madding and Walters<sup>255</sup> review the clinical and laboratory findings in their series of cases of lymphosarcoma of the stomach. The average age was 47 years, and males were affected six times more frequently than females. The lesion occurred most commonly along the lesser curvature, on the posterior wall or at the pylorus. The duration of symptoms varies from a few months to several years. The typical pain is similar to that of gastric ulcer but is less amenable to medical therapy. The occurrence of an epigastric mass or of gross melena is rare. Achlorhydria or hypochlorhydria is usually present, and examination of the blood commonly reveals a milder anemia than that encountered in cases of gastric carcinoma. Diagnostic roentgen studies may not differentiate lymphosarcoma from carcinoma. The authors believe that radical surgical intervention may effect a cure in the lymphocytoma type but that roentgen ray therapy has only palliative effect. The reticulum cell sarcoma is not favorably influenced by irradiation. Giere<sup>256</sup> reemphasizes the lack of a pathognomonic roentgen appearance of gastric lymphosarcoma, which may have serious consequences, since he feels that prognosis in cases of early stages of the disorder in which treatment consists of surgical intervention and irradiation is better than that in cases of early gastric carcinoma. The author presents his observations in a case in which the diagnosis was based on gastroscopy. Ritter<sup>257</sup> describes a lymphosarcoma which involved two thirds of the stomach. Shulman<sup>258</sup> reports a case of primary lymphosarcoma of the jejunum in which about 4 feet (120 cm.) of intestine was involved. Radical surgical treatment and radiation therapy were instituted, but death ensued five months later from a leakage of the anastomosis. At necropsy no sign of local recurrence was encountered. Schaaf and Kraemer<sup>259</sup> present the first recorded case of lymphosarcoma at the ileocecal valve. The commonest sites for this tumor in the large bowel are the cecum and the rectum, according to Hayes, Burr and Pruitt.<sup>260</sup> They describe a case of benign lymphoma of the rectum in which a

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255. Madding, G. F., and Walters, W.: Lymphosarcoma of Stomach, *Arch. Surg.* **40**:120 (Jan.) 1940.

256. Giere, C. N.: Lymphosarcoma, Diagnosed Gastrosopically, *J. A. M. A.* **117**:173 (July 19) 1941.

257. Ritter, S. A.: Case of Primary Lymphosarcoma Occupying Two-Thirds of the Lumen of the Stomach, *Am. J. Surg.* **47**:131, 1940.

258. Shulman, S.: Primary Lymphosarcoma of Jejunum, *Am. J. Roentgenol.* **46**:182, 1941.

259. Schaaf, R. A., and Kraemer, M.: Lymphosarcoma of Ileocecal Valve, *Rev. Gastroenterol.* **7**:248, 1940.

260. Hayes, H. T.; Burr, H. B., and Pruitt, L. T.: Lymphoid Tumors of Colon and Rectum: Report of Case of Simple Lymphoma of the Rectum, *Surgery* **7**:540, 1940.

confusing diagnostic problem was presented. The difficulty of differentiating rectal lymphosarcoma and rectal carcinoma is emphasized by Lynch and Hamilton.<sup>261</sup> These authors believe that rectal lymphosarcoma arises from the submucosal layer of the bowel wall, with early thickening of and lateral spread through this layer. Later invasion and destruction of the muscular and the subserous layer occur. Adhesions to surrounding structures may then follow, but usually the lines of cleavage are easier to identify than in cases of rectal carcinoma. The relative incidence in the rectum of lymphosarcoma and carcinoma is 1:200.

Vieta and Craver<sup>236</sup> describe six types of intrathoracic lesion encountered on roentgen examination of patients with lymphosarcomatous disease. They include: (1) mediastinal involvement; (2) parenchymal infiltration; (3) isolated lesions in the parenchyma of the lung; (4) discrete nodes at the roots of the lung; (5) pleural thickening, and (6) pleural effusion. Of their large series of cases of lymphoblastoma and leukemia, definite intrathoracic pathologic changes occurred in 54 per cent of the cases of lymphosarcoma, 74 per cent of the cases of Hodgkin's disease, 72 per cent of the cases of lymphatic leukemia and 18 per cent of the cases of myelogenous leukemia. They emphasize the extreme variability of the lesions and the lack of a pathognomonic roentgen picture. The authors warn that successful palliation depends on adequate roentgen ray therapy of the widespread, deeper lesions, as well as of those which can be seen or felt. Figoli and Menchaca<sup>262</sup> discuss the symptoms and types of mediastinal tumor, with special emphasis on lymphosarcoma, and Kaufman<sup>263</sup> presents a case of a 3 year old boy with a mediastinal lymphosarcoma, probably of thymic origin.

A case of primary lymphosarcoma of the spleen is reported by Bonney.<sup>264</sup> In spite of surgical removal of the spleen, metastases soon occurred in the liver and spinal cord, with the development of a syndrome of transverse myelitis.

Harrington and Miller<sup>265</sup> present 2 cases of primary lymphosarcoma of the female breast. Since lymphoid tissue does not usually occur in breast tissue, these authors assume a preexisting pathologic change which

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261. Lynch, J. M., and Hamilton, G. J.: Lymphosarcoma of the Rectum, *Tr. Am. Proct. Soc.* **40**:221, 1939.

262. Figoli, C., and Menchaca, F. J.: Síndrome mediastinal por sarcoma linfoblástico (consideraciones acerca de los tumores de mediastino), *Arch. argent. de pediat.* **16**:43, 1941.

263. Kaufman, B.: Lymphosarcoma of Mediastinum Probably of Thymus Origin in a Three Year Old Boy, *Arch. Pediat.* **57**:274, 1941.

264. Bonney, C. W.: Primary Malignant Tumors of the Spleen with Report of a Case of Lymphosarcoma, *J. Lab. & Clin. Med.* **26**:630, 1941.

265. Harrington, S. W., and Miller, J. M.: Lymphosarcoma of Mammary Gland, *Am. J. Surg.* **48**:346, 1940.



results in lymphoid accumulations. Surgical intervention and irradiation are suggested as therapeutic measures.

Gall, Morrison and Scott<sup>266</sup> described the enormous enlargement of the lymph nodes which occurs in the follicular type of malignant lymphoma. Here the normal architecture is replaced by multiple follicle-like nodules; the capsule is involved, and the sinuses are obscured. In a study of 63 cases the authors found that the neoplasm tended to occur in a somewhat older age group than that in which other forms of lymphosarcoma are observed. Retroperitoneal and mesenteric nodes were frequently involved, and splenomegaly occurred in one third of the cases. Hematologic and cutaneous abnormalities were rare.

Combes and Bluefarb<sup>267</sup> have studied 15 cases of giant follicular adenopathy. They feel that the condition is amenable to roentgen ray therapy in its early phase but that the untreated process may develop into lymphosarcoma, Hodgkin's disease or lymphatic leukemia. Baehr and Klemperer<sup>268</sup> describe the onset of this disease as a painless swelling of lymph nodes and spleen without general systemic manifestations. The microscopic pathologic picture of the lymph nodes is described, and the frequency of serous or chylous effusions is emphasized. Late in the disease widespread metastases, including osseous involvement, may occur. This type of tumor is extremely susceptible to irradiation.

The variability of the clinical picture produced by reticuloendothelial neoplasms is described by Budd.<sup>269</sup> This is attributed to the wide distribution of the reticuloendothelial system throughout the body. The lymph nodes may show marked lymphocytic hyperplasia (lymphocytoma), or on the other hand, there may be extensive proliferation of the reticulum cells (reticulum cell sarcoma). When both reticulum cells and lymphocytes are hyperplastic, the disorder may closely resemble Hodgkin's disease. Severe leukocytopenia or frank leukemia may be associated with this type of neoplasm. The reticuloendothelial cells may become differentiated into the monocytic form of leukemia, which may be either of the Schilling or of the Naegeli type. Single or multiple bone lesions are sometimes observed in neoplasms of the reticuloendothelial system.

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266. Gall, E. A.; Morrison, H. R., and Scott, A. T.: Follicular Type of Malignant Lymphoma: Survey of Sixty-Three Cases, *Ann. Int. Med.* **14**:2073, 1941.

267. Combes, F. C., and Bluefarb, S. M.: Giant Follicular Lymphadenopathy: Association of Giant Follicular Lymphadenopathy and Its Polymorphous Cell Sarcoma Derivative, Symmers' Disease, with Lesions of the Skin, *Arch. Dermat. & Syph.* **44**:409 (Sept.) 1941.

268. Baehr, G., and Klemperer, P.: Giant Follicle Lymphoblastoma: Benign Variety of Lymphosarcoma, *New York State J. Med.* **40**:7, 1940.

269. Budd, J. W.: Neoplasms of the Reticulo-Endothelial Tissues, *California & West. Med.* **55**:84, 1941.

Moore and Weller,<sup>270</sup> in a brief review of the literature, state that most patients with lymphosarcoma die within three years of the onset of the primary symptoms. They usually die within one year after bony lesions are diagnosed. Bony metastases are found exclusively in cases of reticulum cell sarcoma, according to previous surveys. A case of lymphosarcoma is reported in which a four year period of "quiescence," or remission, followed the first course of roentgen ray therapy.

In considering the irradiation therapy of lymphoblastomas, Arons<sup>271</sup> feels that the reticuloendothelial system plays a major role in the resistance of the organism to the spread of the malignant growth. Roentgen ray therapy should aim to protect the cells of this system in order to keep the tumor localized. He advises the use of frequent fractionated doses in order to kill tumor cells already injured by previous roentgen ray treatment. Roberts,<sup>272</sup> on the other hand, feels that large doses of roentgen rays should be employed in an effort to cause local fibrosis and sclerosis of such density that the lymphosarcomatous growth cannot spread.

Progress in experimental studies of lymphomas is evidenced by frequent additions to the literature. During the past year Adamstone<sup>273</sup> has reported the occurrence of reticulum cell sarcoma in chicks following intestinal ulceration induced by a dietary deficiency of vitamin E. The spontaneous appearance of similar tumors has been noted in a colony of rats by Nelson and Morris.<sup>274</sup> Curtis and Dunning<sup>275</sup> are studying a transplantable lymphosarcoma of the mesenteric lymph nodes in rats.

*Leukemia.*—Kaufmann and Lowenstein<sup>276</sup> have defined acute leukemia as a fatal disease of short duration characterized by the unregulated proliferation of primitive leukocytes in the hemopoietic tissue of the bone marrow, lymph nodes and spleen, with delivery of these cells to the peripheral blood in greater or lesser numbers. Infiltration or metaplasia or both may occur in a wide variety of tissues and organs. In the authors' series of 40 cases the age distribution

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270. Moore, C., and Weller, G. L., Jr.: Quiescent Interval and Bone Metastases in Lymphosarcoma, *Am. J. Roentgenol.* **43**:211, 1940.

271. Arons, I.: Further Studies on Radiotherapy of Lymphoblastoma, *Radiology* **37**:164, 1941.

272. Roberts, F.: Lymphosarcoma, *Brit. J. Radiol.* **12**:667, 1939.

273. Adamstone, F. B.: Reticulum Cell Sarcoma Following Ulceration of Intestine in Vitamin E-Deficient Chicks, *Arch. Path.* **31**:717 (June) 1941.

274. Nelson, A. A., and Morris, H. J.: Reticulum Cell Lymphosarcoma in Rats, *Arch. Path.* **31**:578 (May) 1941.

275. Curtis, M. R., and Dunning, W. F.: Transplantable Lymphosarcomata of Mesenteric Lymph Nodes of Rats, *Am. J. Cancer* **40**:299, 1940.

276. Kaufmann, J., and Lowenstein, L.: A Study of the Acute Leukoses, *Ann. Int. Med.* **14**:903, 1940.

covered the first four decades. In half of their cases the patients at the onset of the disease were 25 or older. This is not in agreement with the usual experience concerning the age incidence of this dyscrasia. Weakness, bleeding tendencies, anorexia, joint pain, fever, sore throat and general malaise were the commonest symptoms. On physical examination, 60 per cent of the patients showed glandular enlargement; 60 per cent, splenomegaly, and about 50 per cent, hepatomegaly. Involvement of the thorax and of bones was frequently noted. The average duration of the disease in this series was ten weeks. In 98 per cent of the cases the patients had anemia at the initial examination, and in 84 per cent there was definite thrombopenia. Roentgen therapy was without benefit in the 9 cases in which it was instituted. The authors express their belief that acute leukemia is due to a maturation abnormality.

Doan and Reinhart<sup>277</sup> found that of their series of 317 cases of leukemia, the disease was myeloid in 33 per cent, lymphocytic in 50 per cent and monocytic in 16 per cent. They were particularly interested in the little understood basophile cell. Cases of myelogenous leukemia with terminal basophilic granulocytosis and primary basophilic leukemia are presented in detail. In a third case both eosinophilic and basophilic granulation within the same cell were noted as a terminal event of myelogenous leukemia. These workers assert that in myelogenous leukemia all three types of granulocytes are hyperplastic but the eosinophils and basophils are more resistant to therapy and may remain elevated in the peripheral blood even during periods of remission.

Beard<sup>278</sup> suggests division of the lymphatic leukemias into two groups—those representing true malignant growths and those representing maturation disturbances. The former group is subdivided into (1) lymphosarcoma, in which little peripheral blood change is noted; (2) leukosarcoma of the Sternberg type, in which sarcoma cells escape into the peripheral blood, and (3) aleukemic leukolymphosarcoma, which occupies a position midway between the two growths just mentioned. The maturation disturbance is described as an arrest similar to that which occurs in pernicious anemia. The abnormal cells then escape into the peripheral blood. The question of an unknown specific deficiency is given attention.

Meyer<sup>279</sup> discusses the pathologic changes in the genitourinary tract associated with leukemia. He states that this tract is involved in 60 to

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277. Doan, C. A., and Reinhart, H. L.: Basophil Granulocyte; Basophilcytosis, and Myeloid Leukemia, Basophil and "Mixed Granule" Types: Experimental, Clinical and Pathological Study, with Report of New Syndrome, *Am. J. Clin. Path.* **11**:1, 1941.

278. Beard, M. F.: Lymphatic Leukemia, *Kentucky M. J.* **39**:138, 1941.

279. Meyer, L. M.: Pathology of the Genitourinary Tract in Leukemia. *Urol. & Cutan. Rev.* **45**:693, 1941.

80 per cent of all patients with the disease. The kidneys may show diffuse or nodular infiltration, while masses at the hilus resembling bone marrow may be present. The bladder may present scattered infiltration throughout the wall, and mucosal hemorrhages may be observed cystoscopically.

Pernokis and Freeland<sup>280</sup> have made detailed chemical studies on the blood of 9 patients with myelogenous leukemia and 4 patients with lymphatic leukemia. They found the total lipoids and the fatty acid fractions to be elevated, while the proteins were slightly depressed, with some increase in the globulin fraction. In most instances the values for nonprotein nitrogen, cholesterol, calcium, protein and amino acid were normal.

Lucia<sup>281</sup> in an excellent article has extensively reviewed the therapeutic armamentarium for combating the leukemias. Farrar<sup>282</sup> has likewise contributed a good review of the commoner therapeutic agents. Dowdy and Lawrence<sup>283</sup> stress the need for individualization of therapy. They suggest the use of small doses of roentgen rays (25 to 50 r) and present their technic in detail. They feel that although the life span of the patient is not affected, there is increased comfort during therapy with small doses and a somewhat more rapid convalescence after treatment. Rubenfeld and Scott<sup>284</sup> emphasize once again that as far as treatment is concerned the total white cell count assumes secondary importance with respect to the welfare of the patient. Popp and Watkins<sup>285</sup> call attention to the fact that chronic lymphatic leukemia may enter a phase in which the typical cell is a large or medium-sized lymphocyte (macrolymphocytosis or mesolymphocytosis). These investigators feel that such cell types are extremely sensitive to irradiation and advise cautious use of roentgen ray therapy lest too precipitous a drop in the total white cell count be produced. This "phase" of leukemia is admittedly rather rare. Livingston and Moore<sup>286</sup> have studied a

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280. Pernokis, E., and Freeland, M. R.: Blood Chemistry Observations in Leucemias, *J. Lab. & Clin. Med.* **26**:1310, 1941.

281. Lucia, S. P.: Leukemia: Evaluation of Therapy, *California & West. Med.* **55**:1191, 1941.

282. Farrar, G. E., Jr.: Chronic Lymphatic Leukemia, *Internat. Clin.* **1**:78, 1941.

283. Dowdy, A. H., and Lawrence, J. S.: Treatment of Chronic Leukemia by Small Dose Roentgen Ray Technic, *J. A. M. A.* **116**:2827 (June 28) 1941.

284. Rubenfeld, S., and Scott, L. D.: X-Ray Therapy of Leukemias, *Radiology* **36**:352, 1941.

285. Popp, W. C., and Watkins, C. H.: Roentgen Therapy for Chronic Macrolymphocytic and Mesolymphocytic Lymphatic Leukemia, *Radiology* **37**:160, 1941.

286. Livingston, K. E., and Moore, R. D.: Reaction of Leukemic Patients to Sulfapyridine Administration: Preliminary Report, *New England J. Med.* **223**:975, 1940.

small series of patients with myeloid and with lymphatic leukemia who were treated with sulfapyridine. In 3 cases of lymphatic leukemia they observed a rapid fall of white cell counts within twelve to eighteen hours after the administration of the drug, the effect lasting several days. The decline involved a decrease in the number of lymphocytes, without any evidence of associated neutropenia. The diseased lymph nodes also showed a reaction in the form of further swelling followed by temporary shrinkage. The authors suggest the possibility that roentgen ray therapy might be more efficacious if administered during these periods of local reaction. No similar effect was noted in cases of myeloid leukemia. Considerable interest is being displayed in the use of the radioactive isotope of phosphorus in the therapy of leukemia. Some of the more important studies concerning this agent are summarized in a special section.

It is impossible to include in this review a summary of all case reports which have appeared in the recent literature. Several of unusual interest, however, are mentioned here. Sterne, Schiro and Molle<sup>64</sup> report the case of a patient who died of myelogenous leukemia four and one half years after a diagnosis of pernicious anemia had been made. The patient responded satisfactorily to liver therapy until the leukemia made its appearance. The authors did not attempt to relate the two illnesses, expressing the belief that they were coincidental. Kemp and Williams<sup>287</sup> reported a case of chloroma in which marked involvement of the meninges overlying both the spinal cord and the brain was noted at autopsy. Pyonephrosis superimposed on chronic myelogenous leukemia developed in a patient observed by Humble.<sup>288</sup> After early death autopsy disclosed a heterotopic focus of bone marrow at the renal hilus causing obstruction to urinary outflow. This focus of marrow contained immature red and white cells in various developmental stages as well as megakaryocytes.

The controversy over the origin and the developmental status of the monocyte is reflected in the paper by Hall and Watkins,<sup>289</sup> who report the case of a 23 year old woman who gave a five year history of loss of weight, fever and a mass in the left upper quadrant of the abdomen. Over a three month period of observation following a course of roentgen ray therapy, the blood picture changed from that of typical myelogenous leukemia to that of a monocytic dyscrasia. In this period the monocyte count rose from 0 to 93 per cent. Death occurred nine months later.

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287. Kemp, T. A., and Williams, E. R.: Chloroma, *Brit. J. Radiol.* **14**:157, 1941.

288. Humble, J. G.: Heterotopic Bone Marrow in the Renal Hilum Causing Pyonephrosis in an Adult with Chronic Myeloid Leukemia, *J. Path. & Bact.* **53**:147, 1941.

289. Hall, B. E., and Watkins, C. H.: Myelogenous Leukemia Changing to Monocytic Leukemia: Report of Case, *Am. J. Clin. Path.* **11**:443, 1941.

The authors believe this to be a case of the Naegeli type of monocytic leukemia. Walsh and Medlar<sup>290</sup> report a case of acute myelogenous leukemia, which they had first believed to be of monocytic type. They suggest that many cells termed monocytes may really be small (thrombocytic type) megakaryocytes. White,<sup>291</sup> on the other hand, believes all monocytes are variants of lymphocytes and feels that the criteria used to classify cells as monocytic are not clearcut.

Friedenberg<sup>292</sup> does not share the view that oral surgical operations are contraindicated for patients with myelogenous leukemia and reports 11 instances of such operations performed without sequelae.

Vallino<sup>293</sup> and Acuña and Vallino<sup>294</sup> report cases of leukemia in children in which both parents had positive serologic reactions for syphilis. One of their patients was a 3 month old boy whose skeletal roentgenograms showed definite bony lesions of syphilis. Pallor had been noted at birth, and at 3 months of age the patient presented petechial hemorrhages, splenomegaly and hepatomegaly. The peripheral blood and the bone marrow contained large numbers of immature white cells which were not classifiable. They believe this to be a case of congenital leukemia in the production of which syphilis may have played a leading role. Vallino states that in her experience most leukemia in children occurs in those whose parents are syphilitic. (Observations of any striking coincidence of leukemia and syphilis have not been reported in the United States or Europe.)

The experimental production of leukemia in animals affords an excellent opportunity for increasing the present meager knowledge of this disease and of the malignant growths as a group. Morton and Mider<sup>295</sup> have applied methylcholanthrene and 3,4-benzpyrene to the skin of mice, with subsequent development of leukocytosis (50,000 to 100,000 white cells per cubic millimeter). Ninety per cent of the cells resembled lymphoblasts. These cells appeared in the blood two to four weeks before lymphadenopathy was recognizable. Furth<sup>296</sup> has also produced mouse leukemia by the use of carcinogenic agents and presents

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290. Walsh, J. C., and Medlar, E. M.: Acute Myelogenous Leukemia, *Am. J. Cancer* **40**:447, 1940.

291. White, E.: A Case of Monocytic Leukemia, *M. J. Australia* **2**:167, 1941.

292. Friedenberg, M.: Myelogenous Leukemia and Its Influence upon Post-operative Healing: Dental Study with Report of One Case, *J. Am. Dent. A.* **28**:943, 1941.

293. Vallino, M. T.: Leucemia mieloside en un niño de 3 meses, *Prensa méd. argent.* **28**:194, 1941.

294. Acuña, M., and Vallino, M. T.: Leucemia congénita aguda, *Arch. argent. de pediat.* **16**:407, 1941.

295. Morton, J. J., and Mider, G. B.: Some Effects of Carcinogenic Agents on Mice Subject to Spontaneous Leukoses, *Cancer Research* **1**:95, 1941.

296. Furth, J., and Barnes, W. A.: Differences Between Malignant Blood Cells from Induced and Spontaneous Leukemias of Mice, *Cancer Research* **1**:17, 1941.

data on genetic studies of his strains of mice. Law<sup>297</sup> used 0.5 per cent 9,10-dimethyl-1,2-benzanthracene in his experiments on mice. Of 119 animals, lymphomatosis occurred in 101, while myeloid leukemia developed in 8 and monocytic leukemia in 2. There was a latent period of about three and one-half months before the blood dyscrasias appeared. Young mice were found to be more susceptible than older animals. In 30 per cent of the controls leukemia developed spontaneously. Engelbreth-Holm and Lefèvre<sup>298</sup> have likewise noted acceleration of neoplastic growth by dimethylbenzanthracene. Sturm<sup>299</sup> has been able to produce resistance in host animals (rats) by injection of living embryonic cells from 18 day old (Wistar rat) embryos. Doljanski, Goldhaber and Pikovski<sup>300</sup> in their studies on fowl leukosis have found that the causative agent can be inactivated by adequate doses of roentgen rays.

The depressant action of colchicine on cell mitosis is well established. The maturation arrest usually occurs at the metaphase stage, with resultant production of bizarre forms called "colchicine figures." Paul, Brown and Limarzi<sup>301</sup> state that after administration of colchicine leukocytopenia occurs first, followed by leukocytosis. Because of the mitotic arrest produced by colchicine the drug was given a therapeutic trial in a patient with myelogenous leukemia. Forty-eight milligrams was administered intramuscularly over a period of six weeks. The downhill course of the illness appeared unaffected. At autopsy degeneration of cells in lymphatic tissue, with bizarre nuclear changes, was noted. While these appeared to be characteristic of the colchicine effect, they could not be considered specific for this drug. In the normal tissues no mitotic abnormalities were noted.

In a short article Hamilton-Paterson<sup>302</sup> submits photographic evidence for his statement that 'mitosis is comparatively common in the bone marrow and in other tissues of persons suffering with monocytic leukemia.

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297. Law, L. W.: Induction of Leukemia in Mice Following Percutaneous Application of 9, 10-Dimethyl-1, 2-Benzanthracene, *Cancer Research* **1**:564, 1941.

298. Engelbreth-Holm, J., and Lefèvre, H.: Acceleration of Development of Leukemias and Mammary Carcinomas in Mice by 9, 10-Dimethyl-1, 2-Benzanthracene, *Cancer Research* **1**:102, 1941.

299. Sturm, E.: Induced Resistance to a Transplantable Lymphatic Leukemia in Rats, *Cancer Research* **1**:627, 1941.

300. Doljanski, L.; Goldhaber, G., and Pikovski, M.: Inactivation of Causative Agent of Fowl Leukosis by X-Rays, *Nature, London* **147**:481, 1941.

301. Paul, J. T.; Brown, W. O., and Limarzi, L. R.: Effect of Colchicine on Chronic Myeloid Leukemia, *Am. J. Clin. Path.* **11**:210, 1941.

302. Hamilton-Paterson, J. L.: Mitosis in Monocytic Leukaemia, *J. Path. & Bact.* **52**:273, 1941.

The leukemoid blood reactions complicating various primary diseases constitute an interesting and often confusing group of blood dyscrasias. Hill and Duncan<sup>303</sup> define a leukemoid state of the peripheral blood as one in which the total white cell count exceeds 50,000 or in which the presence of immature cells is detected. The origin of such a reaction may lie in one of the following processes: (1) bone marrow irritation or stimulation, such as may occur in osteomyelitis, metastatic carcinoma or chronic granuloma or as a reaction to intravenous therapy; (2) liberation leukocytosis, the result of marrow response to overwhelming demand, such as may be associated with acute hemolysis in therapy with sulfanilamide or one of its derivatives, blackwater fever, familial hemolytic anemia, sickle cell anemia, phenylhydrazine therapy, pernicious anemia in crisis and sepsis and also during recovery from granulocytopenia or in impending death from infection, and (3) ectopic hemopoiesis, as in agnogenic myeloid metaplasia. The authors feel that the differential blood count is of definite value in separating leukemoid reactions from true leukemia. In the former disorders, the immature white cells are morphologically normal, myeloblasts usually constitute less than 10 per cent of the total differential count and the numbers of nucleated red cells often bear a direct relation to the degree of white cell immaturity. These conditions generally do not exist in true leukemia. Hadley<sup>304</sup> feels that the leukemoid blood picture results chiefly from a maturation block. Lisa, Solomon and Gordon<sup>305</sup> report a case of leukemoid reaction in the presence of bronchogenic carcinoma with metastases to the bones, liver and spleen. The total white cell count was 28,000, with many immature red cells and white cells, chiefly of the lymphocytic series. Konwaler<sup>306</sup> observed a leukemoid blood reaction in a patient with metastatic melanoma. Over a period of three months the blood picture remained entirely compatible with that of lymphatic leukemia.

Another blood dyscrasia apt to be confused with myelogenous leukemia is that termed by Jackson and his co-workers "agnogenic myeloid metaplasia." Carpenter and Flory<sup>307</sup> list the principal features

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303. Hill, J. M., and Duncan, C. N.: Leukemoid Reactions, *Am. J. M. Sc.* **201**:847, 1941.

304. Hadley, H. G.: Symptomatic Leukemia, *Brit. J. Radiol.* **14**:113, 1941.

305. Lisa, J. R.; Solomon, C., and Gordon, E.: Leukemoid Reaction in Carcinomatous Skeletal and Splenic Metastases: Case Report, *Am. J. Cancer* **40**:227, 1940.

306. Konwaler, B. E.: Metastatic Melanoma with Lymphatic Leukemia Blood Picture, *Am. J. Clin. Path.* **11**:761, 1941.

307. Carpenter, G., and Flory, C. M.: Chronic Non-Leukemic Myelosis: Report of Case with Megakaryocytic Myeloid Splenomegaly, Leukoerythroblastic Anemia, Generalized Osteosclerosis and Myelofibrosis, *Arch. Int. Med.* **67**:489 (March) 1941.



of the disease as (1) osteosclerosis and fibrosis of the marrow cavities; (2) compensatory myeloid tissue in the spleen and the liver, with resultant splenomegaly, and (3) a blood picture characterized by decrease in the erythrocytes, leukocytes and platelets, together with the presence of small numbers of immature red and white cells and occasional megakaryocytes. They suggest that the condition may be the result of hyperplasia of multipotential mesenchymal tissues due to an unknown stimulus. Jordan and Scott<sup>308</sup> point out that little is known of the mechanism of this disorder and classify patients exhibiting such metaplasia into three etiologic groups: (1) those with certain sclerosing tumors and with chemical poisoning (phosphorus, strontium), (2) those with Albers-Schönberg's disease (*Marmor Knochen*) and (3) those with osteosclerosis associated with blood dyscrasias. The authors accept the unitarian view of totipotentiality of the lymphocyte. They suggest that in the presence of gradual consumption of bone marrow by a pathologic process lymphocytes may be stimulated to undergo transformation into specialized blood cells in ectopic foci located in the spleen and lymph nodes. Because of a defective filtration mechanism immature cells escape into the peripheral blood. Hence the metaplasia is compensatory and may overshoot or undershoot the normal blood values in the effort to carry on hemopoiesis. The authors feel that such an explanation would account for the seemingly paradoxical occurrence of polycythemia in a case of atrophy of the bone marrow. Pavlovsky<sup>309</sup> presents a brief account of 9 cases of agnogenic myeloid metaplasia which he has observed. In 1 case the patient died shortly after a course of roentgen ray therapy. In the other 8 the patients were treated conservatively, and all are living. One patient has survived twenty years since the onset of symptoms. Taylor and Smith<sup>310</sup> report the case of a 66 year old man in whom the vertebral, costal and femoral marrow was extensively fibrosed. Ectopic hemopoiesis was encountered at necropsy in the spleen, liver, renal capsules and vestigial remains of hemolymph nodes. No immature red or white cells were noted in the peripheral blood. An excellent review of the prevailing ideas of etiology is appended. Rawson, Parker and Jackson<sup>311</sup> emphasize the possible role of industrial solvents, including benzene and carbon tetrachloride, in the production of myeloid metaplasia. Six patients studied by them gave a history of exposure to such solvents.

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308. Jordan, H. E., and Scott, J. K.: Case of Osteosclerosis with Extensive Extramedullary Hemopoiesis and a Leukemic Blood Reaction, *Arch. Path.* **32**:895 (Dec.) 1941.

309. Pavlovsky, A.: Metaplasia mieloides compensulare de bazo simulando leucemia mieloides subagudes, *Semana méd.* **48**:1459, 1941.

310. Taylor, H. E., and Smith, R. P.: Marrow Sclerosis Associated with Massive Myeloid Splenomegaly, *Arch. Path.* **31**:803 (June) 1941.

311. Rawson, R.; Parker, F., Jr., and Jackson, H., Jr.: Industrial Solvents as Possible Etiologic Agents in Myeloid Metaplasia, *Science* **93**:541, 1941.

*Polycythemia*.—Orten <sup>312</sup> presents a brief account of the history of experimental cobalt polycythemia, stating that it was first reported in 1931. In rats there is an increase in the number of erythrocytes but no concomitant leukocytosis. Such experimental polycythemia has also been produced in dogs, rabbits, pigs, mice, guinea pigs and frogs. In sheep and cattle, and possibly in dogs, cobalt may be necessary for normal hemopoiesis. Although the mechanism of the cobalt effect is not yet completely understood, the element is believed to stimulate the marrow tissue directly, since reticulocytosis occurs before increase of the erythrocyte count. Cobalt may act in some way to interfere with cell respiration and thus call forth a compensatory polycythemia. There is no evidence to support the theory that this type of erythrocytosis develops as a result of decreased blood destruction.

Davis <sup>313</sup> has observed that the increase of blood volume in animals with cobalt polycythemia results primarily from an augmented red cell mass. This author <sup>314</sup> has also found that administration of raw liver or of choline to dogs with cobalt polycythemia depresses the excessive hemopoiesis, as measured by decrease of the reticulocyte count to normal. Hepatic choline is probably responsible for the effect of liver in these experiments. Choline acts in a "muscarine-like" manner, causing better oxygenation of the bone marrow by means of vasodilatation. Another vasodilator, sodium nitrite, likewise caused depression of the excessive blood formation. Decrease in both plasma and cell volume occurred proportionally so that any diluent effect has been ruled out. Conversely, Davis <sup>315</sup> investigated the effects of vasoconstrictor drugs on the erythrocyte count and the hemoglobin level and found that in normal dogs and rabbits a significant rise of the red cell count occurred after administration of ephedrine. In polycythemic rabbits a further increase in the erythrocyte level was observed. In order to exclude increases of circulating erythrocytes attendant on the splenic constriction produced by vasopressor drugs, animals were splenectomized and found to react to ephedrine in a manner similar to that of subjects not operated on. The administration of amphetamine also increased the erythrocyte count consistently in normal dogs but unpredictably in normal rabbits. When-

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312. Orten, J. M.: Experimental Polycythemia, Detroit M. News, Educ. Issue **32**:42, 1941.

313. Davis, J. E.: Blood Volume in Cobalt Polycythemia, Proc. Soc. Exper. Biol. & Med. **45**:671, 1940.

314. Davis, J. E.: Mechanism of the Depressant Action of Liver and Choline Hydrochloride upon Experimental Polycythemia: Effect of Sodium Nitrate and Choline Derivatives on Polycythemic Dogs, J. Pharmacol. & Exper. Therap. **70**:408, 1940.

315. Davis, J. E.: Production of Experimental Polycythemia in Dogs, Rabbits and Man by Daily Administration of Ephedrine; and by Amphetamine in Dogs, Am. J. Physiol. **134**:219, 1941.

ever rises of the hemoglobin level and the red cell count occurred, an increase in reticulocytes was first noted. The effects produced by these vasoconstrictor drugs were only temporary. The blood returned to the preexperimental level seven to ten days after their discontinuance. In a human subject whose blood values were normal, administration of ephedrine caused a rise of 800,000 erythrocytes per cubic millimeter and an elevation of hemoglobin concentration of 11 per cent over a two week period. The leukocytes were not affected. Davis believes that the pressor drugs reduce the blood flow through the bone marrow, with resultant hypoxemia and stimulation of erythropoiesis. Frost, Spitzer, Elvehjem and Hart<sup>316</sup> have noted an inhibition of the hemopoietic effect of iron and copper in anemic animals to which cobalt had been previously fed. Active hemopoiesis was resumed after administration of liver. In their studies of the circulatory adjustments in human beings with polycythemia, Stewart, Wheeler and Crane<sup>316</sup> have observed decrease of the cardiac volume output and increase of the arteriovenous oxygen differential. Both of these variations were proportional to the increase in hemoglobin and in erythrocytes. After effective therapy the values for cardiac volume output and arteriovenous oxygen differential returned to normal. These investigators found the cardiothoracic ratio to be normal in 5 of their 6 patients, while in 1 patient it showed a slight increase. They suggest that the increased viscosity of the blood causes slowing of the circulation, with subsequent increase of the arteriovenous oxygen differential. The relatively slow return of the blood to the heart decreases cardiac output, an effect which is not especially detrimental, since the increased blood hemoglobin of polycythemic patients makes a larger cardiac output unnecessary for the maintenance of adequate fixed tissue oxygenation.

Erickson and her associates<sup>317</sup> have analyzed the chemical composition of the red cell in a small series of polycythemic patients (2 with polycythaemia rubra vera and 1 with polycythemia secondary to a cardiac lesion). In those with primary polycythemia the hemoglobin and the nonhemoglobin protein fraction of the erythrocytes was lower than normal, whereas in the patient with compensatory erythrocytosis these values were within normal limits. The content of total lipids, cholesterol and phospholipids in the red cells was elevated in both types of polycythemia. The composition of the erythrocyte stroma in the red cells of these patients differed from that in red cells of beef embryos in which physiologic erythrocytosis is present.

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316. Stewart, H. J.; Wheeler, C. H., and Crane, N. F.: Circulatory Adjustments in Polycythemia Vera, *Am. Heart J.* **21**:511, 1941.

317. Erickson, B. N., and others: Correlated Hematologic, Physical and Chemical Studies of Blood and Stroma in Polycythemia and Beef Embryo, *J. Lab. & Clin. Med.* **26**:1492, 1941.

Hodes and Griffith<sup>318</sup> present a preliminary report of the differential roentgen findings in the chest in 11 cases of primary and 3 cases of secondary polycythemia. In polycythaemia rubra vera increased truncal shadows and increased markings were seen in the middle and peripheral pulmonary fields, explicable on the basis of pulmonic vascular engorgement. In 3 cases the patients also showed sharply circumscribed lesions in the middle pulmonary zone which had remained unchanged for years. In the secondary type of polycythemia there is absence of change in the truncal shadows and in the middle and peripheral pulmonary zones until congestive failure occurs. Prominence of the hilar shadows and the pulmonic conus and right-sided cardiac hypertrophy may be present in the secondary type of polycythemia as additional differential diagnostic aids.

Holbrook<sup>319</sup> has observed the effects of venesection on 10 polycythemic patients. He states that the decrease in hemoglobin level and red cell count is usually discernible within a few days after venesection but that the full effect may not be realized for five to seven weeks. No reticulocytosis follows venesection. The blood volume changes slightly, although the hematocrit reading decreases approximately 4.5 per cent after withdrawal of 400 cc. The symptomatic benefit of a single venesection may last from a few days to one year, with an average duration of two months.

Stover and Herrell<sup>320</sup> report a case of polycythaemia rubra vera in which there developed thrombosis associated with thrombophlebitis of the right subclavian and the right axillary vein. They believe such extensive thrombophlebitis of the upper extremity is rarely encountered. The treatment of this patient consisted of daily venesection for a short period followed by administration of phenylhydrazine in doses of 0.3 Gm. one day each week.

The recent studies of the use of radioactive phosphorus in the treatment of polycythemia are discussed in the following section.

*Radioactive Phosphorus.*—Since the advent of the cyclotron investigators have had access to radioactive isotopes of several elements which can be used either as "tracers" in the study of the metabolism of these elements or as therapeutic agents. Radioactive phosphorus (isotope P-32) is being extensively used in various types of investigation.

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318. Hodes, P. J., and Griffith, J. Q.: Chest Roentgenograms in Polycythemia Vera and Polycythemia Secondary to Pulmonary Arteriolosclerosis, *Am. J. Roentgenol.* **46**:52, 1941.

319. Holbrook, A. A.: Use of Venesection in Treatment of Erythremia, *Wisconsin M. J.* **40**:899, 1941.

320. Stover, L., and Herrell, W. E.: Extensive Thrombosis of Right Subclavian and Axillary Veins Associated with Thrombophlebitis, Lymphedema and Polycythemia Vera, *Proc. Staff Meet., Mayo Clin.* **15**:817, 1940.

A number of investigators have been studying several phases of phosphorus metabolism with the aid of this isotope, but most of the data concerning the relation of phosphorus to blood dyscrasias have been reported by the group working at the University of California at Berkeley in conjunction with the physicist E. Lawrence. These investigators have studied the effects both of small "tracer" doses of the isotope and of larger therapeutic doses.

To young healthy monkeys <sup>321</sup> single doses of radioactive phosphorus were administered, and the effect on the peripheral blood was noted. The lymphocytes were affected first, a gradual fall being observed a few days after the administration of the agent. The lymphocyte count reached its minimum value after fourteen to twenty days, whereas the granulocytes decreased after between twenty-one and twenty-eight days, and the erythrocytes between thirty-eight and forty-five days. The lethal dose for monkeys was found to be 1.04 millicuries and that for healthy mice 1.37 millicuries per pound of body weight. These quantities represented about ten times the usual therapeutic dose for human beings. Healthy dogs <sup>322</sup> were fed radioactive phosphorus enclosed in rubber so that effects of irradiation of the gastrointestinal lymph tissue might be studied without complicating factors due to absorption of the radioactive substance. It was found that mild lymphocytopenia developed, which might be construed as supportive evidence for the view that the majority of blood lymphocytes originate in the lymph tissues of the gastrointestinal tract.

Comparative studies <sup>323</sup> on the absorption and distribution of radioactive phosphorus in the blood were performed on the blood of normal and of leukemic human subjects. The results indicated that a greater amount of radioactive phosphorus is retained by leukemic than by normal whole blood. The radioactive phosphorus content of plasma reaches a maximum before the second hour after oral administration. It then tapers off to zero on the eighth day. The highest values in the red cells occur between six and twenty-four hours after ingestion and then gradually decline. During the first forty-eight hours after oral administration the content of radioactive phosphorus in the white cells of leukemic patients rises more rapidly to higher levels than is observed in the leukocytes of normal persons. After this early rapid rise the content

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321. Scott, K. G., and Lawrence, J. H.: Effect of Radio-Phosphorus on Blood of Monkeys, *Proc. Soc. Exper. Biol. & Med.* **48**:155, 1941.

322. Erf, L. A.: Note on the Effect of Dermal and Enteral Irradiation by Radio-Phosphorus on the Blood Levels of Dogs, *Am. J. M. Sc.* **202**:650, 1941.

323. Erf, L. A., and Lawrence, J. H.: Clinical Studies with the Aid of Radio-active Phosphorus: I. Absorption and Distribution of Radio-Phosphorus in the Blood and Its Excretion by Normal Individuals and Patients with Leukemia. *J. Clin. Investigation* **20**:567, 1941.

of the isotope continues as a high plateau in the white cells of leukemic patients and a lower plateau in the white cells of healthy persons. This difference may be explained by the more rapid reproduction of white cells or by the elevated phosphorus metabolism of white cells in persons with leukemia. After intravenous administration of the isotope the leukocytes in patients with leukemia retained still larger amounts, whereas in normal subjects the concentration of leukocytes was only slightly greater than when the material was given by the oral route.

Excretion data indicate that 25 to 50 per cent of ingested radioactive phosphorus is eliminated by normal persons during a six day period. After the lapse of forty-eight hours a larger amount is found in the urine than in the feces. Persons with leukemia excreted in a similar period between 5 and 25 per cent, of which the larger part consistently appeared in the feces.

In an investigation of the effects of radioactive phosphorus on patients with polycythemia<sup>324</sup> it was noted that the isotope gradually became incorporated into the phospholipid fraction of the red cells. In the blood plasma the ingested isotope rapidly appeared in the phospholipid fraction and reached a maximum concentration in this fraction between the forty-eighth and the ninety-sixth hour after ingestion, whereas the content of radioactive phosphorus in the acid-soluble fraction rose to a maximum even earlier.

In autopsy specimens obtained from patients who died of lymphatic leukemia and who had been treated with radioactive phosphorus, the highest content of the isotope was found in the liver, ribs, vertebral bodies, sternum, spleen, lymph nodes, testes and kidneys.<sup>325</sup>

Previous animal experiments by these investigators at the University of California at Berkeley showed that phosphorus metabolism was markedly altered in leukemic mice. The absorption and retention of radioactive phosphorus was increased. Recently they have studied the phospholipid, the acid-soluble and the nucleoprotein fraction of various tissues and organs, including lymphoma tissue itself.<sup>326</sup> By killing con-

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324. Erf, L. A., and Lawrence, J. H.: Clinical Studies with Aid of Radio-Phosphorus: Absorption and Distribution of Radio-Phosphorus in the Blood of, Its Excretion by, and Its Therapeutic Effect on, Patients with Polycythemia, *Ann. Int. Med.* **15**:276, 1941.

325. Erf, L. A., and Friedlander, G.: Phosphorus Exchange in Tissues of Patients with Lymphoid Leukemia, *Proc. Soc. Exper. Biol. & Med.* **47**:134, 1941. Erf, L. A.: Retention of Radiophosphorus in Whole and Aliquot Portions of Tissues of Patients Dead of Leukemia, *ibid.* **47**:287, 1941.

326. Tuttle, L. W.; Erf, L. A., and Lawrence, J. H.: Studies on Neoplasms with the Aid of Radioactive Phosphorus: II. Phosphorus Metabolism of Nucleoprotein, Phospholipid and Acid Soluble Fractions of Normal and Leukemic Mice, *J. Clin. Investigation* **20**:57, 1941.

trol and leukemic mice at various intervals after administering "tagged" phosphorus, differences in metabolism of radioactive phosphorus in the two groups of mice could be studied. The control group retained 25 per cent of the administered isotope at the end of seven days, whereas 40 per cent was found in the leukemic mice. Leukemic mice showed increased absorption and retention of radioactive phosphorus by nucleoprotein and acid-soluble fractions in the liver, the spleen and the lymph nodes. The phospholipid metabolism is affected only slightly by the presence of leukemic infiltration. In the lymphoma tissue itself there was rapid incorporation of radioactive phosphorus into nucleophosphate, which is probably related to carbohydrate metabolism in the tumor.

The group working at Berkeley feel that radioactive phosphorus is an effective therapeutic agent in the treatment of leukemia and polycythemia.<sup>327</sup> It is simple to administer, and there are no untoward after-effects of irradiation if frequent, small doses (2 millicuries) are used. They have found radioactive phosphorus to be as effective as roentgen rays in the management of patients with chronic leukemia but just as disappointing in the treatment of those with acute forms of the disease. In patients with polycythemia<sup>324</sup> the response is not so rapid as in ones with leukemia. In 3 patients fairly large doses were required to reduce the hemoglobin content and red cell count. The response became manifest about one hundred days after initiating therapy.

*Myeloma.*—Although osteolytic lesions without generalized osteoporosis are not pathognomonic of multiple myeloma, they are characteristic of the roentgen appearance of the disease, according to Kinney.<sup>328</sup> Metastatic carcinoma and syphilitic lesions of bone give osteoblastic reactions roentgenologically, while generalized osteoporosis is often encountered in hyperparathyroidism. Bence-Jones proteinuria occurs in 50 to 65 per cent of cases of myeloma, and there is evidence of renal damage in 70 per cent. Hyperproteinemia occurs in about half of the cases of multiple myeloma.

Paul and Pohle<sup>329</sup> differentiate solitary bone myelomas into two groups, those which remain localized and those which metastasize, producing the lesions of multiple myeloma. They have reviewed 45 cases of solitary myeloma and find that the dorsal portion of the spine, the pelvis and the femur are the three commonest sites of origin. Males are

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327. Erf, L. A.; Tuttle, L. W., and Lawrence, J. H.: Clinical Studies with the Aid of Radio-Phosphorus: IV. Retention in Blood, Excretion and Therapeutic Effect of Radiophosphorus on Patients with Leukemia, *Ann. Int. Med.* **15**:487, 1941.

328. Kinney, L. C.: Multiple Myeloma, *Radiology* **35**:667, 1940.

329. Paul, L. W., and Pohle, E. A.: Solitary Myeloma of Bone: Review of Roentgenological Features, with Report of Four Additional Cases, *Radiology* **35**:651, 1940.

afflicted three times as frequently as females, and the greatest incidence occurs in the fifth decade of life. The differential roentgen diagnosis of the disease is discussed at length. These authors believe that whenever possible a combination of surgical intervention and roentgen irradiation is the most effective therapy.

Several interesting cases have been reported in the literature during the past year. Kirsch<sup>330</sup> described a patient with solitary myeloma who survived for twelve years. Gilmore<sup>331</sup> encountered laryngeal metastasis in a case of multiple myeloma. Unilateral exophthalmos and dural lesions of the spinal cord were noted by Flynn and Sailer.<sup>332</sup> Absence of Bence-Jones proteinuria throughout the course of illness in a patient with multiple myeloma is reported by Berger and Goodman.<sup>333</sup> They noted some transient clinical improvement after roentgen ray therapy. Bertrand, Fuks and Bonadeo Ayrolo<sup>334</sup> reviewed the pediatric literature and found only 12 cases of multiple myeloma reported in children, to which they added an instance of the disease in an 8 year old boy.

#### BONE MARROW

Study of the bone marrow is assuming an ever increasing importance in the evaluation of blood dyscrasias. In addition, the marrow promises to become an important site for the administration of fluids and drugs in circumstances in which the use of other parenteral routes is not feasible. Tocantins and O'Neill<sup>335</sup> have found the bone marrow to be a suitable pathway for introducing solutions into the general circulation. They report that fifty-two infusions of blood and other materials were administered by them without untoward effects. The quantities varied from 50 to 2,000 cc. and were given by gravity at the rate of 0.4 to 25 cc. a minute. Fluids so introduced leave the medullary space promptly through the emissary veins. In another article Tocantins, O'Neill and Price<sup>336</sup> report the successful use of the intrasternal route for admin-

330. Kirsch, I. E.: Plasma-Cell Myeloma of Bone, of Over Twelve Years' Duration, *M. Bull. Vet. Admin.* **18**:96, 1941.

331. Gilmore, G. B.: Multiple Myeloma with Laryngeal Metastasis, *Arch. Otolaryng.* **34**:453 (Sept.) 1941.

332. Flynn, J. E., and Sailer, S.: Unilateral Exophthalmos and Spinal Cord Compression in a Case of Multiple Myeloma, *Ohio State M. J.* **37**:771, 1941.

333. Berger, S. S., and Goodman, J. I.: Multiple Myeloma: Report of Case, *Ohio State M. J.* **37**:1163, 1941.

334. Bertrand, J. C.; Fuks, D., and Bonadeo Ayrolo, A.: Mielomas múltiples en un niño de 8 años, *Arch. argent. de pediat.* **16**:147, 1941.

335. Tocantins, L. M., and O'Neill, J. F.: Infusions of Blood and Other Fluids into the General Circulation via the Bone Marrow: Technique and Results, *Surg., Gynec. & Obst.* **73**:281, 1941.

336. Tocantins, L. M.; O'Neill, J. F., and Price, A. H.: Infusions of Blood and Other Fluids via the Bone Marrow in Traumatic Shock and Other Forms of Peripheral Circulatory Failure, *Ann. Surg.* **114**:1085, 1941.



istration of fluid to 72 patients with peripheral circulatory collapse. In a third article Tocantins, O'Neill and Jones<sup>337</sup> present results of intramedullary injections into animals. The application of their technic to problems of pediatric therapy is given considerable attention. Macht<sup>338</sup> has observed prompt absorption of the aqueous solutions of several common drugs after injection into the bone marrow of animals. Drugs in oily vehicles were also well absorbed, although at a somewhat slower rate.

Hebbel<sup>339</sup> describes his technic for obtaining and preparing sternal marrow, using heparin as an anticoagulant. He centrifuges the aspirated mixture of blood and marrow and prepares films of the buffy layer. He estimates that the normal erythrocyte-myelocyte ratio varies from 1:1 to 1:3.75. The typical bone marrow findings in various blood dyscrasias, such as pernicious anemia, hemolytic anemia, aplastic anemia, agranulocytosis, purpura and leukemia, are well reviewed. Smith<sup>340</sup> discusses the value of marrow studies in diseases of infancy and of childhood. He believes that examination of the sternal marrow during therapy with sulfanilamide or its derivatives is of value in the early recognition of toxic blood reactions. Nucleated cell counts of the sternal marrow below 100,000 per cubic millimeter indicate danger of continued drug administration, and significant decrease of the more mature marrow elements may also give warning of impending reactions. The author discusses the appearance of the bone marrow punctate in the various types of purpura and in hereditary pseudohemophilia, Gaucher's disease, Niemann-Pick disease and Cooley's anemia.

Israels<sup>341</sup> points out that hemoglobin does not normally appear in the developing red cell until it has reached the late normoblast stage, at which time the nucleus has become pyknotic and the cell has lost its powers of reproduction. In pernicious anemia, on the other hand, hemoglobinization occurs at a much earlier stage of red cell development, appearing before the cell has lost its reproductive potentiality. This type of red cell formation is called megaloblastic erythropoiesis as opposed to the normal, or normoblastic, erythropoiesis. Israels also believes that there may be abnormally early hemoglobinization of the normoblast when

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337. Tocantins, L. M.; O'Neill, J. F., and Jones, H. W.: Infusions of Blood and Other Fluids via Bone Marrow: Application in Pediatrics, *J. A. M. A.* **117**: 1229 (Oct. 11) 1941.

338. Macht, D. I.: Absorption of Drugs Through Bone Marrow, *Proc. Soc. Exper. Biol. & Med.* **47**:299, 1941.

339. Hebbel, R.: Bone Marrow Biopsy, *Minnesota Med.* **24**:442, 1941.

340. Smith, C.: Recent Advances in the Diagnosis and Treatment of Blood Disorders in Infancy and Childhood, *M. Clin. North America* **25**:659, 1941.

341. Israels, M. C. G.: Haemoglobinisation of Erythroblasts, *J. Path. & Bact.* **52**:361, 1941.

there is a sudden demand for erythrocyte production, such as happens in hemolytic anemias. Therefore, early hemoglobinization alone cannot be used in the differentiation of normoblastic and megaloblastic erythropoiesis. He<sup>4</sup> classifies pathologic erythropoiesis into four main types: (1) hyperplastic erythropoiesis with failure of normal proerythroblast maturation (liver deficiency anemia type); (2) hyperplastic erythropoiesis with failure of normoblast maturation (iron deficiency anemia type); (3) hyperplastic erythropoiesis with normal maturation (hemolytic anemia type), and (4) general failure of red cell formation (aplastic anemia type). Most anemias will fall into one of these four categories. Schwind<sup>342</sup> maintains that the argument concerning the occurrence of megaloblasts in normal bone marrow has arisen because of the difficulty of differentiating megaloblasts from normoblasts by the supravital staining methods and concludes that dried, stained films are superior for examining the bone marrow in hyperchromic macrocytic anemias.

Castrodale and his associates<sup>343</sup> have noted hyperplasia of the bone marrow, especially of the myeloid series, after administration of large doses of diethylstilbestrol and estradiol to dogs. The hyperplasia was followed by a phase of hypoplasia. Megakaryocytes were reduced in numbers and appeared shrunken. These changes coincided with the appearance of hemorrhagic tendencies in the experimental animals. The amounts of diethylstilbestrol used were one hundred times greater than the ordinary therapeutic dose.

Blumenthal<sup>344</sup> has found that when homoisotransplants of various mouse tumors grow to a large size the animals may become debilitated and anemic and may display hyperplasia both of erythrocyte and of granulocyte elements in the bone marrow.

Other articles dealing with the role of marrow in hemopoiesis and the changes produced by disease are considered under the appropriate section headings of this review.

#### SPLENIC DISORDERS

*Banti's Syndrome.*—Whipple and associates<sup>345</sup> have continued their studies of the internal circulation of the spleen in relation to splenomegaly.

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342. Schwind, J. L.: Study of Megaloblast Problem with Supravital Method, *Anat. Rec.* **79** (supp. 2):55, 1941.

343. Castrodale, D.; Bierbaum, O.; Helwig, E. B., and MacBryde, C. M.: Comparative Studies of the Effects of Estradiol and Stilbestrol upon the Blood, Liver, and Bone Marrow, *Endocrinology* **29**:363, 1941.

344. Blumenthal, H. T.: Effects of Spontaneous and Transplanted Rat and Mouse Tumors on Red and White Cells in Circulating Blood and Bone Marrow, *Cancer Research* **1**:196, 1941.

345. Whipple, A. O.: Recent Studies in Circulation of Portal Bed and of the Spleen in Relation to Splenomegaly (Thomas Dent Mütler Lecture), *Tr. & Stud., Coll. Physicians, Philadelphia* **8**:203, 1941.

It is their contention, based on microscopic study of living mammalian spleens, that the splenic pulp spaces provide the only circulatory link between the arterial and the venous system. Within the pulp spaces, blood is stored, filtered and phagocytosed and the red cells are subjected to hemolytic action.

In a discussion of Banti's syndrome the author maintains that the clinical and pathologic course of the disease is a result of mechanical circulatory obstruction within the portal venous bed leading to engorgement of the spleen and splenomegaly. Studies of the pressure of the blood within the splenic vein made at the time of splenectomy showed increases of two to five times that of the peripheral venous pressure. Such obstruction may be intrahepatic or extrahepatic. The intrahepatic type may be caused by Laennec's cirrhosis, by cardiac decompensation with periportal scarring or by blocking of portal vein radicles by parasites. Extrahepatic obstruction may result from traumatic or inflammatory scarring involving the portal bed. In children congenital stenosis of the splenic vein has been encountered. In cases of splenomegaly due to extrahepatic obstruction, cirrhosis of the liver will not develop after splenectomy if a normal liver is present at the time of operation. The occurrence of hematemesis subsequent to the removal of the spleen depends on the site of the obstruction of the portal bed which caused the splenomegaly. Only in cases of disorders affecting the splenic vein will subsequent prevention of hematemesis result; in other types of extrahepatic, and in intrahepatic, obstruction portal hypertension will eventually ensue. The histopathologic picture of spleens removed from patients with "portal hypertension" includes, characteristically, widening and distention of veins, with resultant compression of the pulp spaces, and fibrosis at the periphery of the follicles due to hemorrhages from back pressure as the blood passes from the arterial capillaries into the pulp.

Pregnancy complicating splenic anemia has been reviewed by Robins,<sup>346</sup> who found only 12 cases reported in the literature between 1918 and 1940. Three cases, of which 1 was fatal, of hemorrhages from the cervix during the postpartum period were noted. Five patients underwent splenectomy during pregnancy, and in 2 instances both mother and child died at delivery or soon thereafter.

The results of splenectomy in patients with Banti's syndrome are given by Wada.<sup>347</sup> Of a series of 17 patients, the operative mortality was highest in those with advanced hepatic damage. Several patients,

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346. Robins, S.: Splenic Anemia Complicating Pregnancy: Review of Literature and Case Report, *Virginia M. Monthly* **68**:86, 1941.

347. Wada, S.: Remote Postoperative Results in Thirty-Three Cases of Splenectomy, *Okayama-Igakikai-Zasshi* **53**:1711, 1941.

despite severe impairment of hepatic function, lived more than three years after splenectomy. Otuka<sup>348</sup> feels that splenectomy is justified by the increase in life expectancy. Of 24 patients who survived the postoperative period, 5 lived more than ten years. Splenectomy should be done early to prevent subsequent hepatic damage, according to this author. Cruz<sup>349</sup> feels that splenectomy is indicated if dangerous hemorrhage exists, even in the presence of ascites and hepatic damage. The best results, however, may be expected if the liver is unimpaired. Haden<sup>350</sup> believes the operation should be done in cases of portal congestion and bleeding varices and in the face of evidence of bone marrow depression. He reports that only 2 of 9 patients with preoperative gastrointestinal bleeding who survived operation for one year or more remained permanently free from hemorrhage. The author followed up 21 patients after splenectomy. Six patients died as an immediate result of the operation; 2 died in less than one year, 1 from pulmonary embolism and 1 from cerebral hemorrhage, and 4 suffered fatal gastrointestinal hemorrhages occurring five to seven years after splenectomy. Six other patients survived in good health for one to ten years after operation. Haden also considers splenectomy of value in certain cases of cirrhosis of the liver associated with splenomegaly.

The hematologic changes following splenectomy were carefully studied in 19 patients by Singer, Miller and Dameshek.<sup>351</sup> These include the presence of Howell-Jolly bodies and target cells in the peripheral blood. Many of the red cells are abnormally thin, which accounts for their increased resistance to hypotonic solution of sodium chloride. Fecal output of urobilinogen was decreased, and the lysolecithin content of the peripheral blood was low. The authors describe a "hyposplenic state" characterized by the findings just mentioned which occurs in patients with atrophy of the spleen and contrast this condition with the "hypersplenic state" associated with leukocytopenia, thrombopenia and increased fragility of red cells. The possibility in these two conditions of a reciprocal relation of the spleen and the bone marrow is pointed out.

*Gaucher's Disease.*—The results of splenectomy performed during the course of Gaucher's disease are reviewed by Logan,<sup>352</sup> who discusses

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348. Otuka, T.: Resultate der Splenektomie bei der sogenannten Banti'schen Krankheit, Zentralbl. f. Chir. **68**:307, 1941.

349. Cruz, R.: Anemia esplénica o enfermedad de Banti, Rev. méd. de Chile **69**:303, 1941.

350. Haden, R. L.: Selection of Cases for Splenectomy, Illinois M. J. **79**:421, 1941.

351. Singer, K.; Miller, G. B., and Dameshek, W.: Hematologic Changes Following Splenectomy in Man, with Particular Reference to Target Cells, Hemolytic Index and Lysolecithin, Am. J. M. Sc. **202**:171, 1941.

352. Logan, V. W.: Results of Splenectomy in Gaucher's Disease, Surg., Gynec. & Obst. **72**:807, 1941.

1 case of his own and 7 others previously reported. He concludes that the operation is justified by the observed results. He noted striking clinical improvement, including cessation of hemorrhage, decreased size of the liver, lessened cutaneous pigmentation and gain in body weight. The preoperative leukocytopenia was replaced by persistent leukocytosis. A decreased incidence of infections of the upper respiratory tract was observed, and there were no deaths from acute intercurrent pulmonary infections. The mortality rate from splenectomy was about 15 per cent.

Christianson<sup>353</sup> administered pure cerebroside intraperitoneally to rabbits and after an interval observed lipid deposits in the liver, spleen and lymph nodes similar to but less extensive than those encountered in cases of Gaucher's disease.

*Niemann-Pick Disease.*—Niemann-Pick disease is reviewed by Maurer,<sup>354</sup> who compiled 58 cases reported in the literature since 1914, when the syndrome was first described. The high incidence of the disease in members of the Jewish race, its insidious onset in early life and its fatal termination within two and one-half years are emphasized. The blood findings include anemia and leukocytosis, vacuolization of lymphocytes and high plasma contents of cholesterol, lipid phosphorus and fatty acids. Splenomegaly and hepatomegaly are consistently present. No successful therapeutic measure is known, and splenectomy and irradiation with radium are of little value. The author observed 4 cases and reports the necropsy observations in 3.

#### HEMORRHAGIC DISORDERS AND BLOOD COAGULATION

*General Observations.*—The hemorrhagic diatheses are classified as to causation by Haden and Schneider.<sup>355</sup> In 74 of 310 cases of abnormal bleeding, purpura was observed without a deficiency of platelets. In these cases an increased capillary permeability is suggested by the authors as the important factor in abnormal bleeding. Allergy, rheumatic disease and renal disease were the most common causes of nonthrombopenic purpura in this group. Abnormal blood coagulation is given by the authors as an additional important factor in the causation of hemorrhagic diatheses.

Perlman and Fox<sup>356</sup> analyzed 355 cases in which anatomic evidence of hemorrhagic diathesis was encountered at necropsy, an incidence of

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353. Christianson, O. O.: Experimental Lesions Produced by Cerebroside, *Arch. Path.* **32**:369 (Sept.) 1941.

354. Maurer, L. E.: Niemann-Pick's Disease: Report of Four Cases, *Rocky Mountain M. J.* **38**:460, 1941.

355. Haden, R. L., and Schneider, R. W.: The Hemorrhagic Diathesis: Review of Three Hundred and Ten Cases, *Am. J. Clin. Path.* **11**:263, 1941.

356. Perlman, L., and Fox, T. A.: Hemorrhagic Diathesis: Analysis of Three Hundred and Fifty-Five Autopsy Reports, *Arch. Int. Med.* **68**:112 (July) 1941.

3.4 per cent in the 10,355 autopsy records studied. These authors classified the cases into 4 groups according to the cause of the hemorrhagic diathesis: (1) platelet deficiencies, 22 per cent; (2) abnormalities of the capillary walls, 66 per cent; (3) abnormalities of the clotting elements of the blood, 10 per cent, and (4) miscellaneous causes, 2 per cent. An altered capillary permeability occurred with infectious states in 50 per cent of all cases studied in which there was a hemorrhagic diathesis. Among the infectious conditions, bacterial endocarditis was the greatest offender, followed by meningitis, septicemia and pneumonia. The toxins of nephritic origin produced capillary damage and abnormal bleeding in 16 per cent of all cases, an incidence almost equal in importance to that of primary blood dyscrasias.

Kracke,<sup>357</sup> Witts<sup>358</sup> and Moloney<sup>359</sup> emphasize the importance of diagnostic laboratory procedures in the study of hemorrhagic disorders. Haden and Schneider<sup>355</sup> point out that three organs or tissues must be carefully evaluated in every clinical coagulation problem: the liver, which supplies prothrombin, fibrinogen and heparin; the bone marrow, which forms platelets to furnish thromboplastin, and the blood vessels, which may vary in permeability.

The ability of cutaneous capillaries to withstand rupture can be measured by the application of negative pressure to a localized cutaneous area. Using the suction cup method, Franke<sup>360</sup> obtained abnormally low resistance values in patients with obstructive jaundice. A return to normal occurred after treatment with vitamin K. A modification of the suction cup method has been devised by Reid<sup>361</sup> which allows the study of individual capillary loops under direct microscopic vision. Vacek<sup>362</sup> believes that the administration of vitamin P increases capillary resistance if low initial values exist. Vitamin P has been successfully employed by Rapaport<sup>363</sup> to correct abnormally low capillary fragility in allergic children. This vitamin has also been employed with apparent success by Goldfarb<sup>364</sup> in the treatment of psoriasis. No effect

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357. Kracke, R. R.: *Diagnosis and Treatment of Purpuric Diseases*, South. M. J. **34**:56, 1941.

358. Witts, L. J.: *The Bleeder and the Laboratory*, *Lancet* **1**:642, 1941.

359. Moloney, W. C.: *Clinical Classification and Diagnosis of Hemorrhagic Diatheses*, *New England J. Med.* **225**:933, 1941.

360. Franke, H.: *Die Wirkung des Vitamin K auf die Capillarresistenz beim Okklusionsikterus*, *Klin. Wchnschr.* **20**:212, 1941.

361. Reid, J.: *Capillary Resistance Test*, *Glasgow M. J. (supp.)* **136**:49, 1941.

362. Vacek, V.: *Neuere Erkenntnisse über Vitamin P*, *Schweiz. med. Wchnschr.* **71**:155, 1941.

363. Rapaport, H. G.: *Vitamin P and Capillary Fragility*, *J. Pediat.* **18**:321, 1941.

364. Goldfarb, A. E.: *Treatment of Psoriasis with Lemon Citrin (Vitamin P), Citrin Lemonade and Ascorbic Acid*, *Arch. Dermat. & Syph.* **43**:536 (March) 1941.

of vitamin P on edema associated with pregnancy was observed by Shute.<sup>365</sup> The oral administration of vitamin P was followed by cessation of bleeding and marked increase in capillary resistance in a case of severe purpura associated with measles which was encountered by Miller.<sup>366</sup>

Rocha e Silva and Dragstedt<sup>367</sup> found that capillary permeability was increased by the injection of tissue extracts. The amount of increase bore a direct relation to the amount of histamine contained in such extracts. Engel<sup>368</sup> noted decreased capillary permeability in dogs, cats and rabbits after severance of sympathetic nerves, despite postoperative vasodilatation.

Glanzmann and collaborators<sup>369</sup> report a case of congenital lack of fibrinogen in a 3 year old boy. There was a tendency to bleed, with giant hematoma characterized by fluid contents. The bleeding and coagulation time of the blood was prolonged. In contrast, in acquired fibrinopenia of childhood there occur jaundice, hepatomegaly, splenomegaly, "streak-like" cutaneous hemorrhages and altered hepatic function. Three patients with a chronic hemorrhagic diathesis characterized by a prolonged bleeding time were studied by Carpenter and Allen.<sup>370</sup> The authors demonstrated differences in the nature of the clots produced in vitro when recalcified plasma from the patients and from control subjects was allowed to coagulate in the presence of a dilute thromboplastin solution. In the pathologic plasma the clot was small and consisted of tenuous threads which rapidly contracted into a firm mass of fibrin. Control plasma from normal persons yielded large clots which underwent only moderate contraction. The authors attribute these differences to deficiency in the "natural thromboplastin" content in the plasma and believe they contribute to the observed bleeding tendency.

*Essential Thrombopenic Purpura.*—Haden and Schneider<sup>355</sup> report 18 cases of the idiopathic form with platelet counts below 120,000 per

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365. Shute, E.: Use of Vitamin P in Oedema of Pregnancy Toxaemia, *Canad. M. A. J.* **45**:542, 1941.

366. Miller, A. A.: Purpura in Course of Measles: Case Treated with Vitamin P, *Brit. J. Child. Dis.* **38**:1, 1941.

367. Rocha e Silva, M., and Dragstedt, C. A.: Nature of the Capillary Permeability Factor Present in Extracts of Normal Tissues, *Proc. Soc. Exper. Biol. & Med.* **46**:303, 1941.

368. Engel, D.: Influence of Sympathetic Nervous System on Capillary Permeability, *J. Physiol.* **99**:161, 1941.

369. Glanzmann, E.; Steiner, H., and Keller, H.: Konstitutionelle angeborene Afibrinogenämie und Fibrinopenia im Kindesalter, *Schweiz. med. Wchnschr.* **70**: 1243 and 1261, 1940.

370. Carpenter, G., and Allen, J. G.: Defect in Clot Formation Observed in Three Cases of Chronic Agnogenic Hemorrhagic Disease, *Am. J. M. Sc.* **202**:655, 1941.

cubic millimeter. Clot retraction was absent and bleeding time was prolonged in each instance. The coagulation time was prolonged in 7 cases. The authors state in interpreting their data :

It is evident from these figures that the vascular permeability component of the platelets was lacking in all while the thromboplastin factor was lacking in a much smaller number.

Kelly <sup>371</sup> observed a 12 year old girl with purpura, menorrhagia and a platelet count below 10,000 per cubic millimeter for a period of fourteen months without noting any significant change despite roentgen ray therapy over the spleen. Splenectomy was followed by thrombocytosis (over 1,500,000 cells per cubic millimeter). The platelets fell subsequently to a level of 55,000 per cubic millimeter and remained at this level. Despite the low platelet count the menses remained normal. Napier and Das Gupta <sup>372</sup> failed to observe any significant change in the platelet count or the hemorrhagic tendency of a patient with essential thrombopenia after roentgen ray therapy over the spleen, injection of snake venom and oral administration of vitamins K, C and P. Dressler <sup>373</sup> gave vitamin K intravenously to 2 patients with primary thrombopenia and normal prothrombin time and observed a significant but temporary shortening of the bleeding time.

Haden <sup>375</sup> discusses the selection of patients with essential thrombopenic purpura for splenectomy. If the disorder is chronic and there are significant hemorrhagic manifestations, the operation is indicated. In certain cases of the acute form of the disease splenectomy should also be performed. The author reports good results after removal of the spleen in 7 patients with thrombopenic purpura. Wilensky <sup>374</sup> is in general agreement with Haden's views. Reis <sup>375</sup> observed a patient for six years after splenectomy and did not note any recurrence of abnormal bleeding.

After the original report of Troland and Lee that lowering of the platelet counts followed injection into animals of extracts prepared from the spleens of patients with thrombopenic purpura, evidence both in substantiation and in refutation of their conclusions has been offered

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371. Kelly, T. C.: *Thrombocytopenic Purpura*, Pennsylvania M. J. **44**:1442, 1941.

372. Napier, L. E., and Das Gupta, C. R.: *A Case of Acute Thrombocytopenic Purpura*, Indian M. Gaz. **76**:282, 1941.

373. Dressler, M.: *Ueber die Wirkung des Vitamins K (Synkavit) auf die Blutungszeit bei Thrombozytopenien*, Schweiz. med. Wchnschr. **71**:483, 1941.

374. Wilensky, A. O.: *Indications for Splenectomy in Association with Anemia and Splenomegaly*, Surgery **9**:99, 1941.

375. Reis, E.: *Beitrag zur Splenektomie bei Purpura haemorrhagica*, Zentralbl. f. Chir. **68**:1043, 1941.



by others. Otenasek and Lee<sup>376</sup> support the original work by the report of a significant fall in the platelet counts of rabbits following the intravenous injection of splenic extracts, although in some instances thrombocytosis followed the initial thrombopenia. Confirmatory reports are presented by Rose and Boyer,<sup>377</sup> who gave splenic extracts from 2 patients with purpura intravenously to rabbits, and also by Watson,<sup>378</sup> who observed similar results with three splenic extracts. This author did not observe any consistent alteration in the platelet counts when the extracts were given intraperitoneally to rats. Colmer and Mersheimer,<sup>379</sup> employing two splenic extracts administered according to the method of Troland and Lee, were unable to observe a consistent decrease of the platelet counts in rabbits.

Leonard and Falconer<sup>380</sup> report that purpuric manifestations are not consistently produced in guinea pigs in spite of severe reduction of platelet counts. The thrombopenia was produced by the administration of antiplatelet serum. Guinea pigs on vitamin C-deficient diets treated similarly did not differ from normal animals in the manifestation of purpura. The authors concluded that a deficiency of vitamin C did not contribute to increased capillary permeability in thrombopenic animals. They suggest that a functional rather than an anatomic abnormality of the endothelium might be the major factor in the causation of thrombopenic purpura. Kopeloff and Kopeloff<sup>381</sup> studied the blood platelet levels of animals during anaphylactic shock. A significant lowering of platelet counts occurred in monkeys and other animals after the injection of various antigens. After desensitization of the same animals to the original antigens, a similar degree of thrombopenia developed despite the absence of any anaphylactoid reaction. The authors concluded that the depression of the platelet count is a specific reaction to an antigen not altogether associated with anaphylaxis.

Uihlein and Kendrick<sup>382</sup> noted a progressive fall in the number of circulating platelets in dogs during the course of development of surgical

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376. Otenasek, F., and Lee, F. C.: Further Observation on Thrombocytopen, *J. Lab. & Clin. Med.* **26**:1266, 1941.

377. Rose, H., Jr., and Boyer, L. B.: Thrombocytopen: Confirmatory Report, *J. Clin. Investigation* **20**:81, 1941.

378. Watson, G. M.: Blood Platelets and Splenic Extracts, *Brit. M. J.* **1**:704, 1941.

379. Colmer, M. L., and Mersheimer, W. L.: Relation of Splenic Extracts to Etiology of Essential Thrombopenia, *Arch. Surg.* **43**:422 (Sept.) 1941.

380. Leonard, M. E., and Falconer, E. H.: Experimental Thrombocytopenia Purpura in Guinea Pig, *J. Lab. & Clin. Med.* **26**:648, 1941.

381. Kopeloff, N., and Kopeloff, L. M.: Blood Platelets in Anaphylaxis, *J. Immunol.* **40**:471, 1941.

382. Uihlein, A., and Kendrick, D. B., Jr.: Determinations of Blood Platelets During Traumatic Shock: Experimental Study, *Proc. Staff Meet., Mayo Clin.* **16**:161, 1941.

shock. Splenectomy did not alter the results. Castrodale and collaborators<sup>343</sup> found that in dogs massive doses of estradiol and diethylstilbestrol led to bleeding and thrombopenia. The latter agent was less effective, and the dose required to produce purpura was one hundred times the maximum therapeutic dose for human beings.

From experimental studies Wright<sup>383</sup> concluded that the decrease of blood platelets observed in vitro was due to adhesion of the thrombocytes to the walls of the container. A section of the glass wall of the container was removed and stained and a platelet count was made. A direct relation was observed between the number of platelets on the glass wall and their disappearance from the blood.

*Secondary Thrombopenic Purpura.*—In the series of cases reported by Perlman and Fox<sup>356</sup> leukemia, aplastic anemia and multiple metastases to the bone marrow were the most frequent causes of secondary thrombopenia encountered at necropsy. Haden and Schneider<sup>355</sup> found the bleeding time prolonged in all but 2 of 26 cases and the coagulation time prolonged in over one half of the cases. Two cases of thrombopenic purpura occurring after the ingestion of acetylisopropylacetylcarbamide (sedormid) are reported by Schäfer,<sup>384</sup> and a case occurring after the ingestion of quinine is recorded by Bais.<sup>385</sup> Burke<sup>386</sup> reports 10 instances of thrombopenia occurring in a series of 3,250 patients during treatment with sulfarsphenamine for venereal diseases. Stephenson, Chambers and Anderson<sup>387</sup> noted 2 deaths in one year in the United States Navy due to blood dyscrasias resulting from the use of arsenical compounds in the treatment of venereal infection. In 1 fatal case agranulocytosis developed after the administration of neoarsphenamine and bismuth subsalicylate; in the other malignant granulocytopenia and thrombopenia with hemorrhage from the nasal membrane occurred after administration of neoarsphenamine and mercury inunctions. A total of 129,295 injections of arsenical compounds were administered during the year. Kirkham and Perlmutter<sup>388</sup> report 1 fatal case of

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383. Wright, H. P.: Adhesiveness of Blood Platelets in Normal Subjects with Varying Concentrations of Anticoagulants, *J. Path. & Bact.* **53**:255, 1941.

384. Schäfer, H.: Thrombopenische Blutungen nach wiederholten Sedormid-Gaben, *Med. Klin.* **36**:1133, 1940.

385. Bais, W. J.: Another Case of Thrombopenic Purpura Caused by Quinine, *Geneesk. tijdschr. v. Nederl.-Indië* **81**:2177, 1941.

386. Burke, E. T.: Blood Dyscrasia in the Treatment of Venereal Diseases, *Brit. J. Ven. Dis.* **17**:125, 1941.

387. Stephenson, C. S.; Chambers, W. M., and Anderson, L. T.: Toxic Effects of Arsenical Compounds as Employed in Treatment of Diseases in the United States Navy, 1939, *U. S. Nav. M. Bull.* **39**:139, 1941.

388. Kirkham, D., and Perlmutter, M.: Fatal Aplastic Anemia Following Use of Mapharsen: Case Report, *Arch. Dermat. & Syph.* **43**:111 (Jan.) 1941.

granulocytopenia together with absence of platelets after mapharsen therapy. Weiner and Carter<sup>389</sup> report an instance of thrombopenic purpura associated with miliary tuberculosis of the spleen. Splenectomy was followed by a rise in the platelet count to 500,000 per cubic millimeter and complete recovery of the patient. Thrombopenia associated with discoid lupus erythematosus is reported by Edelman.<sup>390</sup>

*Nonthrombopenic Purpura.*—Henoch's purpura is discussed by Hampton,<sup>391</sup> who observed in 2 patients exacerbations of the syndrome after the ingestion of specific foods and regressions when these foods were eliminated from the diet. Gastrointestinal roentgenograms revealed changes in the functional activity of the bowel which paralleled the clinical course of the illness. One of the 2 patients studied obtained relief from the syndrome after administration of a 1:1,000 solution of epinephrine hydrochloride. González Batlle<sup>392</sup> reports 2 instances of generalized purpura, hematuria and gastrointestinal bleeding following Mantoux tests on a series of 3,000 children. He chose to classify them as instances of allergic purpura due to sensitivity to tuberculin. A case of the Schönlein-Henoch type of purpura subsequent to smallpox vaccination was encountered by Weingärtner.<sup>393</sup> Spontaneous recovery occurred. The Waterhouse-Friderichsen syndrome is reviewed by Lindsay and his collaborators,<sup>394</sup> Drummond and Tooke<sup>395</sup> and Monfort and Mehrling.<sup>396</sup> Purpura was a feature in each of the 9 new cases reported in these articles. The sudden onset of fulminating toxemia, rapidly developing and extensive purpura, alternating cyanosis and

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389. Weiner, J. J., and Carter, R. F.: Acute Thrombocytopenic Purpura Hemorrhagica Associated with Tuberculosis (Miliary) of Spleen: Splenectomy—Recovery, *Ann. Surg.* **113**:57, 1941.

390. Edelman, M. H.: Thrombocytopenic Purpura Associated with Discoid Lupus Erythematosus and Renal Glomerular Changes, *Ann. Int. Med.* **15**:116, 1941.

391. Hampton, S. F.: Henoch's Purpura Based on Food Allergy, *J. Allergy* **12**:579, 1941.

392. González Batlle, P.: Púrpura hemorrágica e intradermoreacción tuberculínica, *Bol. Soc. cubana de pediat.* **13**:66, 1941.

393. Weingärtner, L.: Purpura Schönlein-Henoch als Folgeerscheinung einer Erstvakzination, *Kinderärztl. Praxis* **12**:39, 1941.

394. Lindsay, J. W.; Rice, E. C.; Selinger, M. A., and Robins, L.: Waterhouse-Friderichsen Syndrome, *Am. J. M. Sc.* **201**:263, 1941.

395. Drummond, W. F., and Tooke, T. B., Jr.: Waterhouse-Friderichsen Syndrome: Review of Literature and Report of Two Cases, *New Orleans M. & S. J.* **94**:11, 1941.

396. Monfort, J. A., and Mehrling, J. H.: Waterhouse-Friderichsen Syndrome: Review of Literature and Report of Case with Autopsy, *Am. J. Dis. Child.* **62**:144 (July) 1941.

pallor, coma and circulatory collapse with rapidly fatal outcome are emphasized. At necropsy a massive medullary hemorrhage of the adrenal, generally bilateral, is encountered. Meningococci are recovered from the blood stream in a majority of the cases. The therapeutic suggestions of these authors include chemotherapy combined with the use of antimeningococcus serum, administration of epinephrine or of adrenal cortex extract and infusions of physiologic solution of sodium chloride, together with supportive measures. Prompt recognition of this striking syndrome with institution of specific therapy may, it is thought, alter its invariably fatal termination.

Aggeler, Lucia and Thompson<sup>397</sup> discuss primary thrombocytosis and present a syndrome due to occlusion of all arteries arising from the aortic arch which is characterized by thrombocytosis and autohemagglutination. The number of circulating platelets varied between 1,200,000 and 1,500,000 per cubic millimeter. Autoagglutination of red cells was observed at body, room and ice box temperatures.

*Hemophilia.*—The blood findings in this disease are discussed by Quick<sup>398</sup> with particular emphasis on the methods of diagnosis. As a simple diagnostic test he advocates the determination of the clotting time of oxalated plasma. The plasma is centrifuged, and the clotting time of the supernatant fluid is determined after recalcification. For normal plasma the clotting time by this procedure is approximately two minutes, and for normal whole blood the range is between five and eight minutes. By contrast, hemophilic plasma exhibits a prolonged clotting time of three to five minutes or longer, depending in part on the speed of centrifugation. The observed difference in clotting time of the "platelet-free" plasma is attributed to stability of the platelets, which are slow to disintegrate in hemophilic blood. Efforts to control hemorrhage in hemophilic persons after dental extraction are reported. Van Creveld and Hamer<sup>399</sup> applied a coagulation-promoting globulin obtained from cow's plasma to the tooth socket and obtained favorable results. Heskin<sup>400</sup> notes the reports of other observers that a rubber band placed around a tooth will gradually cut through its attachments. Twenty-six teeth were extracted in this manner with little pain and no hemorrhage in patients with hemophilia.

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397. Aggeler, P. M.; Lucia, S. P., and Thompson, S. H.: 'Syndrome Due to Occlusion of All Arteries Arising from the Aortic Arch: Report of Case Featured by Thrombocytosis and Autohemoagglutination, *Am. Heart J.* **22**:825, 1941.

398. Quick, A. J.: Diagnosis of Hemophilia, *Am. J. M. Sc.* **202**:469, 1941.

399. van Creveld, S., and Hamer, R.: Coagulation-Globulin in Hemorrhages After Extraction of Teeth, Especially in Hemophilic Patients, *Am. J. Orthodontics* **27**:628, 1941.

400. Heskin, N.: Extraction in Hemophilia, *Contact Point* **18**:168, 1941.

Oxalic acid given intravenously to 5 hemophilic patients failed to alter the coagulation time, according to Johnson,<sup>401</sup> in contradistinction to the earlier reports of Page, Russell and Rosenthal. Johnson used infusions of "lyophilized" plasma, and de la Maza<sup>402</sup> gave daily small transfusions of whole blood or citrated plasma and observed a shortening of the coagulation time.

*Hereditary Hemorrhagic Telangiectasia.*—Hereditary hemorrhagic telangiectasia was observed by Alban<sup>403</sup> in members of six generations of one family. Of the 19 affected persons, the majority were women. Griggs and Baker<sup>404</sup> noted severe reactions after transfusion in 1 patient in whom the disease was associated with splenomegaly. Gastroscopic and sigmoidoscopic examinations are reported as "negative" despite gastrointestinal bleeding in another patient examined by these authors. Other instances of this disease are reported by several authors.<sup>405</sup>

*Hemostasis and Coagulants.*—The important role of the capillaries in the phenomena of hemostasis is considered by Macfarlane.<sup>406</sup> Experimental evidence indicates that in normal subjects the reaction of the capillaries to damage is immediate dilation, then contraction, followed after a variable interval by secondary dilation. In patients with hemorrhagic states, such as thrombopenia purpura, associated with prolonged bleeding times, an abnormal capillary response was observed in that the capillaries failed to contract after damage. After injury the liberation of "histamine-like" substances accounts for the immediate capillary dilation. The flow of blood effects rapid removal of these substances, and the contraction phase then occurs. This enables coagulation of the escaped blood and secure attachment of the clot to the surrounding tissue. With subsequent dilation of the capillaries, the formed clot in large open wounds or the tissue exudate in small wounds prevents any further bleeding. Hemostasis is therefore initiated by capillary con-

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401. Johnson, J. B.: Effect of Oxalic Acid Given Intravenously on Coagulation Time in Hemophilia, *Proc. Soc. Exper. Biol. & Med.* **46**:496, 1941.

402. de la Maza, V.: Hemofilia, *Rev. chilena de pediat.* **12**:564, 1941.

403. Alban, H.: Hereditary Hemorrhagic Telangiectasia, *Northwest Med.* **40**:86, 1941.

404. Griggs, D. E., and Baker, M. Q.: Hereditary Hemorrhagic Telangiectasia with Gastro-Intestinal Bleeding, *Am. J. Digest. Dis.* **8**:344, 1941.

405. Becker, S. W., and Obermayer, M. E.: Telangiectasia Hemorrhagica Hereditaria (Osler's Disease) and Vitiligo, *Arch. Dermat. & Syph.* **44**:303 (Aug.) 1941. Madden, J. F.: Hereditary Hemorrhagic Telangiectasia, *ibid.* **44**:540 (Sept.) 1941. Dickman, M.: Hereditary Hemorrhagic Telangiectasia, *ibid.* **44**:523 (Sept.) 1941. Blackwood, W.: Two Cases of Benign Cerebral Telangiectasis, *J. Path. & Bact.* **52**:209, 1941.

406. Macfarlane, R. G.: Critical Review: Mechanism of Hemostasis, *Quart. J. Med.* **10**:1, 1941.

traction and then maintained by coagulation. Coagulation alone is incapable of arresting bleeding, and platelets function only after hemostasis has taken place. They accelerate clot formation and promote firm retraction of the coagulum.

In hemophilia and some other conditions, such as fibrinopenia, in which coagulation does not occur or a faulty clot is formed during the period of capillary contraction, bleeding recommences on subsequent capillary dilation. In prothrombin deficiency states, faulty clot formation may be associated with a physiologic defect of the capillaries.

Viper venom was efficacious as a control of recurrent hemorrhage of the vitreous (Pradhan and Patwardhan<sup>407</sup>). Edsall<sup>408</sup> concludes that the effectiveness of venom from Russell's viper is due to its synergistic action with cephalin and tissue extracts. In vitro studies demonstrated an action of the venom independent of that of thrombin, prothrombin and platelet material. Rosenfeld and Rubinstein<sup>409</sup> studied the coagulant action of venom from the Australian tiger snake. The material appeared to convert prothrombin to thrombin, behaving like thromboplastin plus calcium, as it promptly clotted citrated plasma. Clots formed in vitro were firmer and withstood lysis thirty-six hours longer than those obtained with venom from the fer-de-lance and from *Bothrops jararaca*. Venom from *Bothrops jararaca* has been purified by investigators at the Butantan Institute, São Paulo, Brazil, and can be given intravenously.<sup>410</sup>

An active coagulant has been prepared from rabbit plasma by Parfentjev<sup>411</sup> and its potency confirmed by Taylor, Lozner and Adams.<sup>412</sup> This material appears to act directly on fibrinogen to form thrombin independently of calcium or prothrombin. The effects of the globulin fraction employed were studied in animals by Parfentjev and by Bird,

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407. Pradhan, K. N., and Patwardhan, N. G.: Viper Venom in a Case of Recurrent Hemorrhage in the Vitreous, *Indian M. Gaz.* **76**:221, 1941.

408. Edsall, G.: Mechanism of the Coagulant Action of Daboia Venom, *Am. J. Physiol.* **134**:609, 1941.

409. Rosenfeld, S., and Rubinstein, J.: Separation of Coagulant from Toxic Principles of Venom of Australian Tiger Snake: Remarks on Mode of Action of Coagulant, *J. Lab. & Clin. Med.* **27**:45, 1941.

410. New Antihemorrhagic Agent, *Foreign Letters (Brazil)*, *J. A. M. A.* **116**:2521 (May 31) 1941.

411. Parfentjev, I. A.: A Globulin-Fraction in Rabbit's Plasma Possessing a Strong Clotting Property, *Am. J. M. Sc.* **202**:578, 1941.

412. Taylor, F. H. L.; Lozner, E. L., and Adams, M. A.: The Thrombic Activity of a Globulin Fraction Derived from Rabbit Plasma, *Am. J. M. Sc.* **202**:582, 1941.

McSwain, Kauer and Glenn.<sup>413</sup> Intravenous administration to animals was accompanied by toxic reactions and in some cases by intravascular clotting. When given orally the substance was nontoxic and effected reduction of the clotting time. Clinically, its oral use proved effective either in reducing the coagulation time or in stopping hemorrhage in gastrointestinal bleeding and in hemophilia, according to Bird and collaborators. Local use of the globulin fraction by Lozner, McDonald, Finland and Taylor<sup>414</sup> stopped bleeding from tooth sockets in patients with hemophilia and other hemorrhagic diatheses. The application of the material in the form of a stable dry powder controlled bleeding from small cutaneous wounds.

The arrest of hemorrhages from the nasal passage by the local use of salt pork has been reported by Cone.<sup>415</sup> Its advantages include availability and low cost. Its effectiveness is attributed to the thromboplastic content and the ease of introduction and efficiency as a nasal pack. The salt probably plays no part in its hemostatic action. A preliminary report by Quastel and Racker<sup>416</sup> deals with the increased thromboplastic activity of muscle extracts obtained from anoxic areas and from tissue incubated in an oxygen-free atmosphere.

Rabinowitz<sup>417</sup> found that certain amino acids added to the blood of patients with thrombopenic purpura caused normal retraction in vitro. Cystine and methionine were the most effective. The oral administration of cystine failed to produce any significant change in the bleeding tendencies of 2 patients with Werlhof's type of purpura. However, more favorable effects were noted after the use of methionine. Participation of a fat-soluble substance in the normal coagulation of blood is suggested by Macfarlane and his associates.<sup>418</sup>

The mechanism of the fluidity of the menstrual flow was studied by Glueck and Mirsky,<sup>419</sup> who were unable to detect the presence of fibrin-

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413. Bird, R. M.; McSwain, B.; Kauer, G. L., Jr., and Glenn, F.: The Clotting Action of Rabbit-Clotting Globulin, *Proc. Soc. Exper. Biol. & Med.* **48**:730, 1941.

414. Lozner, E. L.; McDonald, H.; Finland, M., and Taylor, F. H. L.: The Use of Rabbit Thrombin as a Local Hemostatic, *Am. J. M. Sc.* **204**:593, 1941.

415. Cone, A. J.: The Use of Salt Pork in Cases of Hemorrhage, *Arch. Otolaryng.* **32**:941 (Nov.) 1940.

416. Quastel, J. H., and Racker, E.: Tissue Anoxia and Blood Coagulation, *Brit. J. Exper. Path.* **22**:15, 1941.

417. Rabinowitz, H. M.: Role of Amino Acids in Clot Retraction; Effect of Methionine in Restoring Normal Clot Retraction and Control of Bleeding in Essential Thrombocytopenia, *Am. J. Surg.* **51**:366, 1941.

418. Macfarlane, R. G.; Trevan, J. W., and Attwood, A. M. P.: *J. Physiol.* **99**:7P, 1941.

419. Glueck, H. I., and Mirsky, I. A.: The Clotting Mechanism of Menstrual Fluid, *Am. J. Obst. & Gynec.* **42**:267, 1941.

ogen, prothrombin, thrombin or any specific anticoagulant in the fluid. Fibrin clots incubated with menstrual blood underwent lysis. The authors suggest that a lytic action takes place on the intrauterine clots, thus accounting for the findings reported. When bleeding from the uterus is excessive, the rate of intrauterine lysis cannot keep up with the hemorrhage and undigested clots are expelled.

Patients with coronary thrombosis were found by Ewing, Cullimore and Blatherwick<sup>420</sup> to have normal plasma clotting times. The only difference observed between the persons with coronary thrombosis and a control group was a longer interval between the appearance of fibrin and the formation of a firm clot. Such observations suggest that patients with such disease may exhibit delayed coagulation rather than a tendency to increased intravascular clot formation.

Extract of adrenal cortex administered to patients before operation and to normal subjects led to a shortening of the coagulation time, averaging 29 and 38 per cent, respectively, according to Reed.<sup>421</sup> The maximum effect occurred in the two hours after administration of the extract, and some measurable changes were still present after twenty-four hours.

*Heparin.*—Heparin is finding an ever increasing field of clinical usefulness, particularly in the prevention of postoperative thrombosis and embolism and in vascular surgery. In two reviews submitting data on over 1,000 cases Murray<sup>422</sup> and Crafoord and Jorpes<sup>423</sup> conclude that the favorable results outweigh the dangers and disadvantages of its use. Other favorable clinical reports are given by Lam,<sup>424</sup> Bauer<sup>425</sup> and Ravdin.<sup>426</sup>

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420. Ewing, M. E.; Cullimore, O. S., and Blatherwick, N. R.: The Plasma Clotting Time and Serum Calcium of Patients Recovering from Attacks of Coronary Thrombosis, *Proc. Soc. Exper. Biol. & Med.* **47**:23, 1941.

421. Reed, F. A.: Natural Adrenal Cortex Extract and the Coagulation of Blood, *Am. J. Surg.* **51**:330, 1941.

422. Murray, G.: Heparin in Thrombosis and Blood Vessel Surgery, *Surg., Gynec. & Obst.* **72**:340, 1941.

423. Crafoord, C., and Jorpes, E.: Heparin as a Prophylactic Against Thrombosis, *J. A. M. A.* **116**:2831 (June 28) 1941.

424. Lam, C. R.: Heparin Administration: Methods and Results in Thirty Cases, *Ann. Surg.* **114**:205, 1941.

425. Bauer, G.: Early Diagnosis of Venous Thrombosis by Means of Venography and Abortive Treatment with Heparin, *Acta med. Scandinav.* **107**:136, 1941; Venous Thrombosis: Early Diagnosis with the Aid of Phlebography and Abortive Treatment with Heparin, *Arch. Surg.* **43**:462 (Sept.) 1941.

426. Ravdin, I. S.: Heparin, *Am. J. M. Sc.* **201**:299, 1941.



The mode of action of heparin has been investigated by Ferguson and Glazko,<sup>427</sup> who express the view that heparin inhibits thromboplastic enzyme activity, resulting in retardation of prothrombin conversion. It is suggested by Chargaff and his associates,<sup>428</sup> on the basis of electrophoretic studies, that heparin reacts with plasma globulins. It is believed that the natural inhibitor in normal blood which prevents clot formation may be a complex formed of heparin and the plasma proteins. Howell<sup>429</sup> restates his suggestion that a heparin-albumin compound is responsible for the normal fluid state of the blood. The presence of this compound is assured by the constant release of heparin into the blood stream.

In summarizing the effects of heparin on blood values other than coagulation, Rigdon and Wilson<sup>430</sup> list increased resistance of red cells to hypotonic solution of sodium chloride, altered sedimentation rate, inhibition of glycolysis and interference with reactions involving complement. They observed that heparin did not affect capillary permeability or interfere with chemotactic or phagocytic activity of the leukocytes of rabbits. The platelet counts in dogs and mice after injection of heparin were studied by Copley and Robb,<sup>431</sup> who observed a reduction in almost every instance. Heparin appeared to have a destructive action on platelets in vitro proportional to its concentration.

*Dicoumarin.*—The hemorrhagic agent present in spoiled sweet clover has been isolated, identified and synthesized. This work, begun in 1934 by Link and his associates, was completed and reported in a series of papers.<sup>432</sup> Animal experimentation and clinical trial with the new synthetic material were instituted almost immediately. The formula assigned

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427. Ferguson, J. H., and Glazko, H. L.: Heparin, Univ. Hosp. Bull., Ann Arbor **7**:27, 1941; Heparin, J. Lab. & Clin. Med. **26**:1559, 1941.

428. Chargaff, E.; Ziff, M., and Moore, D. H.: Studies on the Chemistry of Blood Coagulation, J. Biol. Chem. **139**:383, 1941.

429. Howell, W. H.: Recent Advances in Problem of Blood Coagulation Applicable to Medicine, J. A. M. A. **117**:1059 (Sept. 27) 1941.

430. Rigdon, R. H., and Wilson, H.: Capillary Permeability and Inflammation in Rabbits Given Heparin, Arch. Surg. **43**:64 (July) 1941.

431. Copley, A. L., and Robb, T. P.: Effect of Heparin on Platelet Count in Dogs and Mice, Am. J. Physiol. **133**:248, 1941.

432. Campbell, H. A.; Roberts, W. L.; Smith, W. K., and Link, K. P.: Studies on Hemorrhagic Sweet Clover Disease: Preparation of Hemorrhagic Concentrates, J. Biol. Chem. **136**:47, 1940. Campbell, H. A.; Smith, W. K.; Roberts, W. L., and Link, K. P.: Studies on the Hemorrhagic Sweet Clover Disease: Bioassay of Hemorrhagic Concentrates by Following Prothrombin Level in Plasma of Rabbit Blood, *ibid.* **138**:1, 1941. Campbell, H. A., and Link, K. P.: Studies on Hemorrhagic Sweet Clover Disease: Isolation and Crystallization of Hemorrhagic Agent, *ibid.* **138**:21, 1941. Stahmann, M. A.; Huebner, C. F., and Link, K. P.: Studies on the Hemorrhagic Sweet Clover Disease: Identification and Synthesis of the Hemorrhagic Agent, *ibid.* **138**:513, 1941.

to this hemorrhagic agent is, 3, 3'-methylenebis-(4-hydroxycoumarin), and the simpler term suggested for it is dicoumarin.

Studies on dogs and subsequent investigations on human subjects carried out by Bingham, Meyer and Pohle<sup>433</sup> and Butt and his collaborators<sup>434</sup> have demonstrated that the administration of dicoumarin prolongs the coagulation time of the blood. They found, in confirmation of the earlier work of others, that dicoumarin acts by prolonging the blood prothrombin time. No harmful effects were noted after administration of the material in doses which increased the coagulation time to as much as twenty-three minutes and the prothrombin time from twelve to eighteen seconds. Laboratory procedures failed to indicate disturbances of hepatic or renal function or changes in the corpuscular elements of the blood following the ingestion of effective doses of dicoumarin. Unlike the effects of heparin, those of dicoumarin are not manifest until about twenty-four hours after administration. If repeated doses are given, the prothrombin content of the blood becomes progressively diminished. The effect on the prothrombin resulting from a single dose administered to dogs gradually disappears in five to seven days. Large doses cause a greater delay in the return of the prothrombin to normal, but the initial latent period is unaffected by the size of the dose. Transfusion of blood temporarily restores normal prothrombin and coagulation times, and administration of vitamin K is without effect. When fatal doses were given to dogs, no significant pathologic change was observed in any organ except the frequent occurrence of capillary, arteriolar and venule dilatation.

The possible advantages of dicoumarin as a substitute for heparin will depend on further demonstration of its ability to delay or prevent intravascular clotting. Its merits appear to lie in its prolonged action, its relatively low cost and its effectiveness when administered orally.

*Prothrombin and Vitamin K.*—Pregnancy and the Neonatal Period: The clinical application of results of recent studies on prothrombin and vitamin K has continued to receive much attention. Over one hundred

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433. Bingham, J. B.; Meyer, O. O., and Pohle, F. J.: Studies on Hemorrhagic Agent 3, 3'-Methylenebis-(4-Hydroxycoumarin): Its Effect on Prothrombin and Coagulation Time of Dogs and Humans, *Am. J. M. Sc.* **202**:532, 1941. Meyer, O. O.; Bingham, J. B., and Pohle, F. J.: Effects of Synthetic Dicoumarin 3, 3'-Methylenebis-(4-Hydroxycoumarin) upon the Prothrombin Time and Coagulation Time, *Proc. Central Soc. Clin. Research* **14**:8, 1941.

434. Butt, H. R.; Allen, E. V., and Bollman, J. L.: A Preparation from Spoiled Sweet Clover (3, 3'-Methylenebis-[4-Hydroxycoumarin]) Which Prolongs Coagulation and Prothrombin Time of the Blood: Preliminary Report of Experimental and Clinical Studies, *Proc. Staff Meet., Mayo Clin.* **16**:388, 1941. Barker, N. W.; Butt, H. R.; Allen, E. V., and Bollman, J. L.: Effect of 3, 3'-Methylenebis-(4-Hydroxycoumarin) on Blood Coagulation Factors: Its Probable Clinical Usefulness, *Proc. Central Soc. Clin. Research* **14**:9, 1941.

and fifty articles on the subject appeared in the last year. Recent general reviews of the development and clinical use of vitamin K include those of Stewart,<sup>435</sup> Almquist,<sup>436</sup> Toohey<sup>437</sup> and others.<sup>438</sup> A discussion of experimental hypoprothrombinemia is given by Rhoads, Warren and Panzer.<sup>439</sup> Prothrombin deficiency in the newborn infant has received much comment, and the subject is reviewed by Savage,<sup>440</sup> Smith,<sup>441</sup> Grossman,<sup>442</sup> Snedeker<sup>443</sup> and others.<sup>444</sup>

It has been clearly demonstrated that physiologic hypoprothrombinemia develops in the immediate neonatal period. At birth the prothrombin value averages 70 to 75 per cent of that of normal adults.

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435. Stewart, J. D.: Clinical Significance of Prothrombin Deficiency and Its Treatment, *Ann. Surg.* **114**:907, 1941.

436. Almquist, H. J.: Vitamin K, *Physiol. Rev.* **21**:194, 1941.

437. Toohey, M.: Prothrombin: Its Estimation, Clinical Significance and the Therapy of Hypoprothrombinaemia, *Irish J. M. Sc.*, 1941, p. 509.

438. Freeman, S., and Grodins, F. S.: Recent Studies of Factors Involved in Coagulation, Including Review of Vitamin K, *Surg., Gynec. & Obst.* **72**:417, 1941. Kark, R., and Souter, A.: Hypoprothrombinemia and Avitaminosis in Man, *Brit. M. J.* **2**:190, 1941. Chute, R.: Value of Vitamin K in Treatment of Abnormal Bleeding, *New England J. Med.* **224**:360, 1941. Quick, A. J.: Contribution of Laboratory to Treatment of Hemorrhage, *Illinois M. J.* **79**:346, 1941. Acuña, M., and Lobo, A. A.: Determinación de la protrombina sanguínea: su valor clínico, *Prensa méd. argent.* **28**:1091, 1941.

439. Rhoads, J. E.; Warren, R., and Panzer, L. M.: Experimental Hypoprothrombinemia, *Am. J. M. Sc.* **202**:847, 1941.

440. Savage, H.: Development of Vitamin K and Its Clinical Use in Neonatal Period, *Arch. Dis. Childhood* **16**:67, 1941.

441. Smith, C. H.: Recent Advances in Diagnosis and Treatment of Blood Disorders in Infancy and Childhood, *M. Clin. North America* **25**:659, 1941.

442. Grossman, A. M.: Coagulation Defects in Infancy and Childhood: Frequency of Hypoprothrombinemic States and Their Treatment with Vitamin K, Reclassification of Hemorrhagic Hypoprothrombinemia Neonatorum, *J. Pediat.* **19**:205, 1941.

443. Snedeker, L.: Hemorrhagic Disease of Newborn: Report of Three Hundred and Fifty-Eight Cases, *J. Pediat.* **19**:1, 1941.

444. Quick, A. J.: Prevention of Bleeding in Newborn, *Wisconsin M. J.* **40**:581, 1941. Bustamante, E. W.: Vitamin K y sus aplicaciones en pediatría, *Rev. chilena de pediat.* **1**:47, 1941. Rouhunkoski, M., and Saksela, N.: Hypoprothrombinemia Neonatorum and Its Relations to Vitamin K, *Acta obst. et gynec. Scandinav.* **21**:203, 1941. Ortega, A. R.: La vitamina K y su empleo en clínica: Revisión de la literatura, *Rev. chilena de pediat.* **1**:165, 1941. Norris, R. F., and Bennett, M. C.: Plasma Prothrombin Values of Mothers and Infants at Delivery: Further Studies Including Comparative Values of Umbilical Arteries and Veins, *Surg., Gynec. & Obst.* **72**:758, 1941. Fanconi, G.: Blutungsübel des Kindesalters, die auf einer Störung des Gerinnungsvorganges beruhen, unter besonderer Berücksichtigung des K-Vitamins, *Schweiz. med. Wchnschr.* **71**:185, 1941. Fiechter, N.: Hypoprothrombinämie und hämorrhagische Diathese des Neugeborenen und ihre Beziehungen zum Vitamin K, *Monatschr. f. Geburtsh. u. Gynäk.* **111**:1, 1940.

It falls rapidly, to reach a minimum level between the second and the fifth day of life, and during this period a hemorrhagic disorder may become manifest. Usually a return to the birth level takes place between the fourth and the sixth day, with a subsequent continued rise for about ten to fourteen days. Values equal to those of normal adults may not be reached until one and one half months of age, according to Plum.<sup>445</sup>

A seasonal factor in the incidence of hypoprothrombinemia of newborn infants has been demonstrated by several observers.<sup>446</sup> In general, values tend to be lower during the winter months. Javert and Macri<sup>447</sup> observed an upward trend of the blood prothrombin value throughout pregnancy. Thirty of 200 pregnant women studied by them had prothrombin values which were less than 70 per cent of normal and were regarded by the authors as representing instances of avitaminosis K. Two separate declines of the prothrombin level were observed during pregnancy; the first occurred at about the fourth week, during the period of morning sickness, and was attributed to deficient dietary intake of vitamin K; the second was noted usually during the twenty-eighth week and was presumably explained by the demands of the fetus. The dietary intake of pregnant women was studied by Astrowe and Palmerton<sup>448</sup> in relation to the subsequent prothrombin values of the mothers and their infants. No relation was found between the level of prothrombin of infants and either an adequate or a deficient intake of vitamin K by the mothers.

Vitamin K given to mothers during labor has proved successful in lessening the fall in prothrombin in the neonatal period. The reports of Bohlender and Rosenbaum<sup>449</sup>; Beck, Taylor and Colburn,<sup>450</sup> and others<sup>451</sup>

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445. Plum, P.: K-Vitaminmangel bei Kindern, *Deutsche med. Wchnschr.* **66**:1389, 1940.

446. (a) Salomonsen, L.: Hemorrhagic Disease of Newborn Due to Hypoprothrombinemia, *Nord. med.* **7**:1309, 1940; (b) On the Prevention of Hemorrhagic Disease of Newborn by Administration of Cow's Milk During the First Two Days of Life, *Acta pædiat.* **28**:1, 1940. (c) Huber, C. P., and Shrader, J. C.: Blood Prothrombin Level in Newborn, *Am. J. Obst. & Gynec.* **41**:566, 1941.

447. Javert, C. T., and Macri, C.: The Prothrombin Concentration in Normal Pregnancy, *Am. J. Obst. & Gynec.* **42**:415, 1941.

448. Astrowe, P. S., and Palmerton, E. S.: Clinical Studies on Vitamin K in Newborn Infants, *J. Pediat.* **18**:507, 1941.

449. Bohlender, G. P., and Rosenbaum, W. M.: Antepartum Use of Vitamin K in the Prevention of Prothrombin Deficiency in the Newborn, *J. A. M. A.* **116**:1763 (April 19) 1941.

450. Beck, A. C.; Taylor, E. S., and Colburn, R. F.: Vitamin K Administered to Mother During Labor as Prophylaxis Against Hemorrhage in Newborn Infant, *Am. J. Obst. & Gynec.* **41**:765, 1941.

451. Valentine, E.; Reinhold, J., and Schneider, E.: Effectiveness of Prenatal Administration of 2-Methyl-1, 4-Naphthoquinone in Maintaining Normal Pro-

are representative. Vitamin K was administered orally at periods ranging from five minutes to forty-eight hours prior to delivery. The prothrombin levels at birth were above 90 per cent of the adult normal value, and there was no subsequent decline. The incidence of hemorrhagic manifestation in the series reported by Beck and co-workers was 0.5 per cent of 1,022 infants whose mothers had been given vitamin K during labor. Thirty-seven infants born prematurely were included in this group, and of these, abnormal bleeding occurred in 5.4 per cent. In a control group of 1,037 infants whose mothers had not received vitamin K the incidence of hemorrhage was 2 per cent. The use of vitamin K is particularly indicated when premature birth of the infant is expected, in cases of prolonged labor or when there is a prospect of any operative type of delivery. In these circumstances intracranial hemorrhage is especially likely to occur, according to Ross and Malloy.<sup>452</sup> It is advised by Lawson, Wyvell and Branning<sup>453</sup> that vitamin K be given orally during the last month of pregnancy, but McCready and his associates<sup>454</sup> report that if treatment has been omitted in the days immediately preceding delivery, there is little effect of previous administration on the prothrombin level of an infant. It is generally recommended that every patient in labor should receive vitamin K, either orally or parenterally and that the dose should be repeated every six to eight hours throughout the duration of labor.

Administration of vitamin K to women during labor reduced the incidence of retinal hemorrhages, according to Maumenee, Hellman and Shettles<sup>455</sup> and Pray, McKeown and Pollard.<sup>456</sup> Javert and Macri<sup>457</sup>

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thrombin Level in Infants, *Am. J. M. Sc.* **202**:359, 1941. Mull, J. W.; Bill, A. H., and Skowronska, H.: Effect on Newborn of Vitamin K Given to Mothers in Labor, *J. Lab. & Clin. Med.* **26**:1305, 1941.

452. Ross, S. G., and Malloy, H. T.: Blood Prothrombin in Newborn: Effect of Vitamin K upon Blood Prothrombin and upon Hemorrhagic Disease of Newborn, *Canad. M. A. J.* **45**:417, 1941.

453. Lawson, R. B.; Wyvell, D. B., and Branning, W. S.: Vitamin K in Prevention and Treatment of Hemorrhagic Disease of Newborn, *North Carolina M. J.* **2**:234, 1941.

454. McCready, R. L.; Callahan, E. T., and Grandin, D. J.: Parenteral Vitamin K Therapy in Ante-Partum Women and Its Effects on the Infants' Prothrombin Levels: A Preliminary Report, *Am. J. Obst. & Gynec.* **42**:398, 1941.

455. Maumenee, A. E.; Hellman, L. M., and Shettles, L. B.: Factors Influencing Plasma Prothrombin in Newborn Infants: Effect of Antenatal Administration of Vitamin K on Incidence of Retinal Hemorrhage, *Bull. Johns Hopkins Hosp.* **68**:158, 1941.

456. Pray, L. G.; McKeown, H. S., and Pollard, W. E.: Hemorrhagic Diathesis of Newborn: Effects of Vitamin K Prophylaxis and Therapy, *Am. J. Obst. & Gynec.* **42**:836, 1941.

457. Javert, C. T., and Macri, C.: Prothrombin Concentration and Mineral Oil, *Am. J. Obst. & Gynec.* **42**:409, 1941.

found that the daily use of liquid petrolatum by pregnant women resulted in a lowering of the prothrombin level.

Hemorrhages of the newborn are classified by Edsall<sup>458</sup> as due either to a low prothrombin level or to causes other than defects in the intrinsic coagulation mechanism, such as transitory bleeding from the intestinal tract or rupture of minor blood vessels during delivery. Vitamin K is of specific value in the treatment of hemorrhages due to hypoprothrombinemia. If the blood prothrombin value is 30 per cent of normal, hemorrhage is common, and if the level falls below 15 per cent, bleeding is apt to be severe.

Vitamin K may be administered effectually by oral, intramuscular or intravenous route and can be absorbed through the skin, according to Russell and Page<sup>459</sup> and deBeer and collaborators<sup>460</sup> when applied in an ointment base. Vitamin K introduced into the blood stream causes a rapid rise of prothrombin. A significant elevation is said to occur after thirty minutes, and in twenty-four hours levels of 70 to 100 per cent of normal may be attained in spite of extremely low initial values. Kove and Siegel<sup>461</sup> found that 1 mg. doses produced a maximal prothrombin response. Once a hemorrhagic tendency has become manifest, the immediate parenteral use of vitamin K is advocated by Willumsen, Stadler and Owen<sup>462</sup> and Leidenheimer and Albritton.<sup>463</sup> The advisability of transfusion as supplementary therapy is advised by Arden,<sup>464</sup> Damm<sup>465</sup> and Kove and Siegel.<sup>466</sup> In the replacement of

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458. Edsall, G.: Prothrombin Level in Early Infancy: Its Relation to Hemorrhage and Other Neonatal Disorder, *New England J. Med.* **224**:762, 1941.

459. Russell, H. K., and Page, R. C.: Effect of Topical Application of 2-Methyl-1, 4-Naphthoquinone on Prothrombin Level of Newborn Infants, *Am. J. M. Sc.* **202**:355, 1941.

460. deBeer, E. J.; Drektar, L., and Flusser, B.: Routes of Administration of Material Capable of Acting as Vitamin K, *Proc. Soc. Exper. Biol. & Med.* **46**:535, 1941.

461. Kove, S., and Siegel, H.: Prothrombin in the Newborn Infant: IV. Further Observations on the Prothrombin Response to Intravenous Administration of Water-Soluble Naphthoquinone, *J. Pediat.* **19**:503, 1941.

462. Willumsen, H. C.; Stadler, H., and Owen, P. A.: Comparative Effects of Vitamin K and Whole Blood on Prothrombin Deficiency of Newborn Infant, *Proc. Soc. Exper. Biol. & Med.* **47**:116, 1941.

463. Leidenheimer, H., Jr., and Albritton, A. S.: Studies on Bleeding Tendency and Vitamin K Therapy in Newborn Children, *New Orleans M. & S. J.* **93**:464, 1941.

464. Arden, F.: Hemorrhage, Anemia and Jaundice of Newborn, *M. J. Australia* **2**:343, 1941.

465. Damm, P. N.: Hemorrhagic Diathesis in Newborn in Regard to Treatment with Transfusion, *Ugesk. f. læger* **102**:620, 1940.

466. Kove, S., and Siegel, H.: Prothrombin in the Newborn Infant: II. Prothrombin Response to Water-Soluble Naphthoquinone Administered Intravenously; III. On the Nature of Prothrombin in the Newborn Infant, *J. Pediat.* **18**:764, 1941.

lost blood and the combat of shock, the indications for transfusion are matters for individual decision. That use of transfused blood as a source of prothrombin is not an effective means of elevating the infant's value above the hemorrhagic zone was reported by Lawson<sup>467</sup> and Gellis and Lyon.<sup>468</sup> Plum<sup>445</sup> succeeded in raising the prothrombin level of bleeding infants by only 1 to 20 per cent by means of transfusions of 20 to 40 cc. of blood. The effect lasted twelve to twenty-four hours. Macpherson<sup>469</sup> obtained similar results and noted that after administration of vitamin K alone, the rise in prothrombin in the infant's blood was higher than when the vitamin was used in combination with blood transfusion. Whole blood given intramuscularly or subcutaneously exerted no effect on the prothrombin level according to Willumsen, Stadler and Owen.<sup>462</sup> The intravenous injection of serum was likewise ineffective.

Gellis and Lyon<sup>470</sup> confirmed the observation of Salomonsen<sup>471</sup> that supplementary feeding of cow's milk instituted soon after birth prevents the usual degree of physiologic fall of prothrombin. They found that the earlier evaporated milk was fed, the less was the subsequent decline in prothrombin. These observations are explained by the correspondingly early invasion of the intestinal tract by bacteria which serve as a natural source of vitamin K.

No qualitative differences between the prothrombin of newborn infants and that of adults were detected by Kove and Siegel.<sup>466</sup> By a dilution procedure, identical patterns of lessened activity were obtained both with blood of normal adults and with the blood of infants with hypoprothrombinemia.

No correlation between hypoprothrombinemia and bilirubinemia in the newborn was found by Norris and Bennett.<sup>472</sup>

Most authors in reporting their studies of hypoprothrombinemia of the newborn employ, often with minor modifications, the method of Smith, Quick or Kato for the determination of the prothrombin time.

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467. Lawson, R. B.: Treatment of Hypoprothrombinemia (Hemorrhagic Disease) of Newborn Infants, *J. Pediat.* **18**:224, 1941.

468. Gellis, S. S., and Lyon, R. A.: Effect of Intravenous Injections of Whole Blood on Prothrombin Index of Newborn Infants, *Am. J. Obst. & Gynec.* **42**:519, 1941.

469. Macpherson, A. I. S.: Treatment of Hemorrhagic Disease of Newborn, *Brit. M. J.* **2**:433, 1941.

470. Gellis, S. S., and Lyon, R. A.: Influence of Diet of Newborn on Prothrombin Index, *J. Pediat.* **19**:495, 1941.

471. Salomonsen (footnote 446 *a* and *b*).

472. Norris, R. F., and Bennett, M. C.: Comparison of Prothrombin and Bilirubin Values in Umbilical Artery and Vein at Delivery, *Bull. Ayer Clin. Lab., Pennsylvania Hosp.* **3**:353, 1941.

Bruchsaler,<sup>473</sup> Huber and Shrader,<sup>474</sup> Lawson,<sup>467</sup> Karabin and Anderson,<sup>475</sup> Russell and Page<sup>459</sup> and Innes and Davidson<sup>476</sup> give details of convenient bedside methods employing whole blood. Lung preparations as a source of thromboplastin are used by Bruchsaler and by Huber and Shrader and venom from Russell's viper by the two last-named pairs of authors.

**Obstructive Jaundice and Hepatic Disease:** In the management of jaundiced patients and those with biliary fistula the use of vitamin K has earned a permanent place.<sup>477</sup> In the surgical patient with jaundice avitaminosis K is the result not so much of deficiency disease as of faulty absorption. Coller and Farris<sup>478</sup> emphasize that the aspiration of bile by any suction apparatus leads to defective absorption of vitamin K in the same manner as obstruction of the bile ducts. Allen and Livingstone<sup>479</sup> observed that the prothrombin of the blood did not fall after operations elsewhere than on the biliary tract in which a variety of anesthetic agents were employed. In contrast a sharp postoperative decline was observed in patients with obstructive jaundice. The patients receiving the least preoperative treatment with vitamin K showed the earliest fall. Experimental studies on dogs, according to Allen, Kable and Livingstone,<sup>480</sup> likewise failed to demonstrate any prolongation of the prothrombin time following use of a variety of anesthetic agents. They found chloroform to be the exception, with a reduction of prothrombin values to 75 per cent or more in twenty-four hours.

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473. Bruchsaler, F. S.: Vitamin K and Prenatal and Postnatal Prevention of Hemorrhagic Disease in Newborn Infants, *J. Pediat.* **18**:317, 1941.

474. Huber, C. P., and Shrader, J. C.: Simplified Determination of Blood Prothrombin Levels in Newborn, *J. Lab. & Clin. Med.* **26**:1379, 1941.

475. Karabin, J. E., and Anderson, E. R.: Simplified Micro Test of Plasma Prothrombin, *J. Lab. & Clin. Med.* **26**:723, 1941.

476. Innes, J., and Davidson, L. S. P.: Simple Method of Estimating Prothrombin Capillary Blood, *Brit. M. J.* **1**:621, 1941.

477. Reid, J.: Prothrombin Deficiency in Diseases of Liver and Bile Passages and Its Treatment with Synthetic Vitamin K, *Brit. M. J.* **1**:579, 1941. Reed, G. S.: The Use of Vitamin K in Obstructive Jaundice, *New York State J. Med.* **41**:1653, 1941. Dario Quiroz, J.: Nuestros conocimientos actuales sobre la vitamina K, *Rev. san mil, Asunción* **14**:41, 1940. Tage-Hansen, E.: Aus Forschung und Erfahrung: Ueber K-Avitaminose und ihr Behandlung, *Hippokrates* **12**:141, 1941. Dam, H.: Vitamin K, *Am. J. Pharm. Educ.* **5**:273, 1941.

478. Coller, F. A., and Farris, J. M.: The Management of Jaundiced Patients with Special Reference to Vitamin K, *Surg., Gynec. & Obst.* **73**:21, 1941.

479. Allen, J. G., and Livingstone, H.: Postoperative Hypoprothrombinemia and Anesthesia, *Arch. Surg.* **42**:522 (March) 1941.

480. Allen, J. G.; Kable, V., and Livingstone, H.: Effects of Anesthetic Agents on Prothrombin Concentrations in Experimental Animals, *Anesth. & Analg.* **20**:156, 1941.



It has been noted that the response of prothrombin to vitamin K administration in the presence of intrahepatic disease is poor and is reported by Olwin<sup>481</sup> to be in marked contrast to that occurring in the presence of jaundice with extrahepatic obstruction. Such variations in the response of prothrombin to the administration of vitamin K have been used by Lord and Andrus<sup>482</sup> to differentiate jaundice due to stone, tumor or stricture from that associated with diffuse hepatic disease. The method measures the change of the prothrombin value of the blood in a given period after the parenteral administration of 2 mg. of menadione. Failure to obtain a rise of more than 10 per cent in twenty-four hours from the pretreatment prothrombin level or more than 15 per cent in forty-eight to seventy-two hours is believed to signify intrahepatic disease. The response to vitamin K has been used as the basis of a hepatic function test. The test is a measure of the ability of the liver to produce prothrombin. This function apparently does not parallel the capacity to synthesize hippuric acid. Poor agreement between the results of the two tests is reported by Lucia and Aggeler<sup>483</sup> and Kark and co-workers.<sup>484</sup> Rosenberg and Soskin,<sup>485</sup> in a report on the cephalin-cholesterol flocculation test as a measure of hepatic function, state that 37 to 100 patients with hepatic damage had a decreased prothrombin value, whereas the cephalin-cholesterol procedure tested on the same subjects yielded positive results in 98 per cent.

Miscellaneous Disorders: Hypoprothrombinemia is reported by Mazzini and Meyer<sup>486</sup> in 14 cases of gastric ulcer. Improvement in the bleeding tendency resulted after institution of vitamin K therapy. A specimen of liver for biopsy was taken in one third of the cases, and signs of early cirrhosis or cholecystitis were found in all instances.

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481. Olwin, J. H.: The Differentiation of Surgical Jaundice from Severe Damage of the Liver (Subacute Yellow Atrophy) Clinically Simulating It, *Arch. Surg.* **43**:633 (Oct.) 1941.

482. Lord, J. W., Jr., and Andrus, W. DeW.: Differentiation of Intrahepatic and Extrahepatic Jaundice: Response of the Plasma Prothrombin to Intramuscular Injection of Menadione (2-Methyl-1, 4-Naphthoquinone) as a Diagnostic Aid, *Arch. Int. Med.* **68**:199 (Aug.) 1941.

483. Lucia, S. P., and Aggeler, P. M.: Influence of Liver Damage on Plasma Prothrombin Concentration and Response to Vitamin K, *Am. J. M. Sc.* **201**:326, 1941.

484. Kark, R.; White, F. W.; Souter, A. W., and Deutsch, E.: Blood Prothrombin Levels and Hippuric Acid Excretion Liver Function Test in Liver Disease, *Proc. Soc. Exper. Biol. & Med.* **46**:424, 1941.

485. Rosenberg, D. H., and Soskin, S.: Comparison of Cephalin-Cholesterol Flocculation Test with Various Criteria of Liver Function, with a Note on the Significance of Hyperexcretion of Hippuric Acid, *Am. J. Digest. Dis.* **8**:421, 1941.

486. Mazzini, O. F., and Meyer, G. R.: Vitamin K y cirugía: Modificaciones de la protrombinemia, *Bol. y trab., Acad. argent de cir.* **25**:18, 1941.

Hypoprothrombinemia was encountered by Lord and Andrus<sup>487</sup> in a series of 36 patients with toxic goiter in the postoperative period. The values increased spontaneously to normal within one week after operation.

Plasma prothrombin studies were carried out by Tocantins and Hause<sup>488</sup> on 31 patients with pneumonia. In approximately one half of all patients at some time during the disease the values were less than 50 per cent of normal, with a tendency for the lowest level to occur early in the course of the infection. The responses to treatment with vitamin K were not consistent in the patients tested.

Pulmonary tuberculosis was studied from the viewpoint of the prothrombin content of the blood by Savacool,<sup>489</sup> Sheely,<sup>490</sup> Bauer<sup>491</sup> and Kaplan.<sup>492</sup> Savacool and Sheely state that patients with the disease in active form possess significantly low prothrombin values. The level of the prothrombin appears to bear an inverse relation to the status of patients with pulmonary tuberculosis as measured by clinical and roentgenologic criteria and is a more accurate index of the activity of the disease process than is the sedimentation rate. In patients suffering with hemoptysis lowered prothrombin values were frequently, but not consistently, found. Vitamin K therapy may prove of value in the management of some patients with pulmonary hemorrhage. Kaplan<sup>492</sup> found normal prothrombin values in patients with hemoptysis. Bauer<sup>491</sup> did not observe any parallel between severity of tuberculosis and the degree of hypoprothrombinemia.

Evidence of vitamin K deficiency was found in 9 of 30 patients with tropical sprue studied by Diaz y Rivera.<sup>493</sup> Of three preparations exhibiting vitamin K activity, only menadione appeared capable of maintaining normal prothrombin levels in patients with nontropical sprue, according to Allen.<sup>494</sup>

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487. Lord, J. W., Jr., and Andrus, W. DeW.: Changes in Liver Associated with Hyperthyroidism with Study of Plasma Prothrombin Level in Immediate Postoperative Period, *Arch. Surg.* **42**:643 (April) 1941.

488. Tocantins, L. M., and Hause, W. A.: The Behavior of Plasma Prothrombin in Pneumonia, *Am. J. Clin. Path.* **11**:849, 1941.

489. Savacool, J. W.: Prothrombin Studies in Pulmonary Tuberculosis, *Am. J. M. Sc.* **201**:830, 1941.

490. Sheely, R. F.: Prothrombin Deficiency in Pulmonary Tuberculosis: Clinical Significance in Hemoptysis, *J. A. M. A.* **117**:1603 (Nov. 8) 1941.

491. Bauer, G.: Ueber Hypoprothrombinämie, Blutungsbereitschaft und Hämoptöe bei Lungentuberculose und ihre Beeinflussung durch Vitamin K, *Deutsche med. Wchnschr.* **67**:594, 1941.

492. Kaplan, R. H.: Use of Vitamin K in Hemoptysis in Pulmonary Tuberculosis, *M. Bull. Vet. Admin.* **18**:48, 1941.

493. Diaz y Rivera, R. S.: Prothrombin Time in Tropical Sprue: Analysis of Thirty Cases, *Puerto Rico J. Pub. Health & Trop. Med.* **17**:128, 1942.

494. Allen, J. G.: Comparative Prothrombin Responses to Vitamin K and Several of Its Substitutes in a Case of Nontropical Sprue, *New England, J. Med.* **224**:195, 1941.

Warner, Spies and Owen<sup>495</sup> add supporting evidence to the view that dietary deficiencies of vitamin K severe enough to produce clinical hypoprothrombinemia are rarely encountered. They report that of 48 patients with signs of deficiencies of some part of the vitamin B complex, only 6 possessed prothrombin levels below 80 per cent of normal. In a control group of 37 patients without evidence either of specific vitamin deficiencies or of hepatic disease, 10 had values below 80 per cent of normal.

A case of idiopathic hypoprothrombinemia in a patient first thought to have hemophilia and observed throughout fifteen consecutive hospital admissions is presented by Rhoads and Fitz-Hugh.<sup>496</sup> The marked prolongation of the prothrombin time was not affected by vitamin K administration. In addition, it appeared that a qualitative deficiency of fibrinogen was also present, as evidenced by an unusual resistance to the action of thrombin. There were no evidences of hepatic disease or of excess antithrombin, antiprothrombin or heparin. The authors were unable to identify this condition with any of the known hemorrhagic diatheses.

Abbott and Holden<sup>497</sup> observed hypoprothrombinemia following prolonged vomiting, intestinal intubation and formation of an intestinal fistula. Vitamin K and bile salts proved effective in overcoming the conditioned deficiency. Allen and Vermeulen<sup>498</sup> present evidence of the storage of vitamin K. In a patient with a bile fistula the authors observed a direct relation between the duration of administration of vitamin K and the period that elapsed after withdrawal of the drug before a decline of the prothrombin resulted. Lowering of the prothrombin time may not occur for a month or longer after the institution of a biliary fistula, whereas in cases of obstructive jaundice such a decrease may take place rapidly. These observations are explained, respectively, by storage of vitamin K and by associated hepatic damage.

Pancreatic achylia was produced in cats by Sproul and Sanders,<sup>499</sup> and subsequent lowering of the prothrombin values of the animals was

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495. Warner, E. D.; Spies, T. D., and Owen, C. A.: Hypothrombinemia and Vitamin K in Nutritional Deficient States, *South. M. J.* **34**:161, 1941.

496. Rhoads, J. E., and Fitz-Hugh, T., Jr.: Idiopathic Hypoprothrombinemia—An Apparently Unrecorded Condition, *Am. J. M. Sc.* **202**:662, 1941.

497. Abbott, W. E., and Holden, W. D.: Hypoprothrombinemia in Intestinal Disorders, *Am. J. Surg.* **53**:215, 1941.

498. Allen, J. G., and Vermeulen, C.: Destruction of Prothrombin and Storage of Vitamin K, *Arch. Surg.* **42**:969 (June) 1941.

499. Sproul, E. E., and Sanders, E. K.: Effect of Pancreatic Achylia on Vitamin K Absorption and Prothrombin Time, *Am. J. Physiol.* **135**:137, 1941.

noted. The absorption of two vitamin K compounds through the intestinal tract is reported by Morse and Schmidt<sup>500</sup> in rats without the presence of bile, in bile fistula animals. The absorption was sufficient to elevate the prothrombin values.

**Substances Possessing Vitamin K Activity:** The routes of administration and the effective doses of various vitamin K preparations have been widely studied. To the most active compound, 2-methyl-1,4-naphthoquinone, has been assigned the nonproprietary name menadione.<sup>501</sup> The lethal dose of menadione for rabbits is placed at three to five hundred times the minimum antihemorrhagic dose as determined by chick assay by Fromherz.<sup>502</sup> Oral administration of this substance in patients with hypoprothrombinemia results in a measurable response within one-half to one hour (Anderson, Karabin, Udesky and Seed<sup>503</sup>). Percutaneous administration of a 1 per cent solution of menadione in cod liver oil as used by Fantl and Corkill<sup>504</sup> or in an ointment base as employed by Russell and Page<sup>505</sup> is an effective mode of therapy. The speed of prothrombin response after oral and after parenteral administration has been compared by Tocantins and Jones<sup>505</sup> and Stewart.<sup>506</sup> The adaptation of menadione to intravenous use is discussed by Olwin.<sup>507</sup> He observed no untoward effects after the injection of single doses of 20 mg. or of 2 mg. daily for periods up to three months. A suspension of naturally occurring vitamin K<sub>1</sub> has been prepared in dextrose solution by Seligman, Hurwitz, Frank and Davis.<sup>508</sup> Prolonged therapeutic

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500. Morse, L. M., and Schmidt, C. L. A.: Absorption of 2-Methyl-1, 4-Naphthoquinone and Phthiocol by Bile Fistula Rats, *Proc. Soc. Exper. Biol. & Med.* **46**:415, 1941.

501. Menadione, Nonproprietary Term for the Substance 2-Methyl-1, 4-Naphthoquinone, report of the Council on Pharmacy and Chemistry, *J. A. M. A.* **116**:1054 (March 15) 1941.

502. Fromherz, K.: *Pharmakologische Wirkungen von Vitamin K-Präparaten*, *Ztschr. f. Vitaminforsch.* **11**:65, 1941.

503. Anderson, E. R.; Karabin, J. E.; Udesky, H. L., and Seed, L.: Oral Administration of Synthetic Vitamin K (2-Methyl-1, 4-Naphthoquinone), *Surgery* **9**:361, 1941.

504. Fantl, P., and Corkill, A. B.: Percutaneous Treatment of Vitamin K Deficiency, *M. J. Australia* **2**:540, 1941.

505. Tocantins, L. M., and Jones, H. W.: Hypoprothrombinemia: Effect of Peroral and Parenteral Administration of Synthetic Vitamin K Substitute (2-Methyl-1, 4-Naphthoquinone), *Ann. Surg.* **113**:276, 1941.

506. Stewart, J. D.: Oral and Parenteral Use of Synthetic Vitamin K-Active Substances in Hypoprothrombinemia, *Surgery* **9**:212, 1941.

507. Olwin, J. H.: Intravenous Use of Vitamin K, *J. A. M. A.* **117**:432 (Aug. 9) 1941.

508. Seligman, A. M.; Hurwitz, E.; Frank, H. A., and Davis, W. A.: Intravenous Use of Synthetic Vitamin K<sub>1</sub>, *Surg., Gynec. & Obst.* **73**:686, 1941.

effects were observed after its intravenous administration in large doses. Many other compounds with vitamin K activity exert important anti-hemorrhagic effects.<sup>509</sup>

**Substances Possessing Thromboplastic Activity:** Thromboplastin preparations made by Quick's method and stored in a refrigerator retained their activity for as long as six months, according to a report by Poncher, Ricewasser and Kato.<sup>510</sup> These authors<sup>511</sup> state that when the material was suspended in physiologic solution of sodium chloride it remained potent for one hundred and twelve days. Thromboplastin prepared from the brains of stillborn infants was found by Sherber<sup>512</sup> to keep without loss of activity for periods up to six months after extraction in physiologic solution of sodium chloride. The stability of such material is not adversely affected by extraction and suspension in a 1:40 molar concentration of calcium chloride in physiologic solution of sodium chloride. Owen and Toohey<sup>513</sup> found thromboplastic activity to be unimpaired when macerated brain was suspended in physiologic solution of sodium chloride for periods over thirty days and stored in air-tight containers at refrigeration temperatures. Moena Gomez<sup>514</sup> obtained the most rapid coagulation time for plasma by using 0.03 to 0.05 cc. of 0.5 per cent calcium chloride solution and 0.1 to 0.5 cc. of thromboplastin in place of the concentrations for the prothrombin time technic given by Quick. The optimal coagulation of plasma occurs at a  $p_H$  range of 6 to 8, according to Tanturi and Banfi.<sup>515</sup> They advocate the use of barium sulfate for removing prothrombin from plasma. The resultant prothrombin-free plasma is neutral in reaction and may be

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509. Doisy, E. A.: Antihemorrhagic Compounds, Proc. Staff Meet., Mayo Clin. **16**:293, 1941. Sharp, E. A.; Vonder Heide, E. C., and Good, W. H.: Vitamin K Activity of Menadione and 4-Amino-2-Methyl-1-Naphthol in Hypoprothrombinemia, J. Lab. & Clin. Med. **26**:818, 1941. Stewart.<sup>506</sup> Olwin.<sup>507</sup>

510. Poncher, H. G.; Ricewasser, J. C., and Kato, K.: Relative Stability and Potency of Thromboplastins for Prothrombin Tests, J. Lab. & Clin. Med. **27**:385, 1941.

511. Poncher, H. G.; Ricewasser, J. C., and Kato, K.: Stability of Quick's Thromboplastic Solutions for Prothrombin Tests, Am. J. Clin. Path., Tech. Supp. **11**:110, 1941.

512. Sherber, D. A.: A Technique for Determination of Prothrombin Time, J. Lab. & Clin. Med. **26**:1058, 1941.

513. Owen, T. K., and Toohey, M.: Estimation of Prothrombin, Lancet **1**:724, 1941.

514. Moena Gomez, A.: Algunas observaciones a la técnica de Quick de titulación de la protrombina, Rev. méd. de Chile **69**:580, 1941.

515. Tanturi, C. A., and Banfi, R. F.: Determinación de la protrombina en la sangre, Bol. Inst. clin. quir. **17**:119, 1941.

added to pathologic plasma when dilution is desirable. Ferguson and Glazko<sup>516</sup> demonstrate that a natural antithrombin is present in plasma by obtaining increased yields of thrombins with maximal calcium and thromboplastin concentrations if the prothrombin is diluted. Ferguson<sup>517</sup> shows citrated prothrombin to be stable in the presence of thrombin. The two substances can coexist without mutual destruction.

Additional contributions on the thromboplastic activity of venom from Russell's viper have been published by Page and Russell<sup>518</sup> in America and Crosbie and Scarborough<sup>519</sup> and Hobson and Witts<sup>520</sup> in England. Page and Russell emphasize the standardized nature of the material and its relative stability in the dry state. The determination of the clotting time is facilitated by the clear solution provided by venom as a thromboplastic material. Hobson and Witts use venom in a concentration of 1:20,000. The addition of lecithin proved to accelerate the clotting rate of venom, and in a concentration of 0.5 per cent (5 mg. of lecithin to 1.0 cc. of venom solution) the substance overcomes interference with clot formation due to hemolysis, hyperlipemia and other factors, which delay coagulation if venom alone is the source of thromboplastin. Crosbie and Scarborough confirm the accelerated rate of plasma coagulation by the addition of lecithin to venom.

Miscellaneous Observations: The concentration of plasma prothrombin in normal subjects was studied by Hause and Tocantins.<sup>521</sup> No consistent variation occurs during menstrual cycles. They give tables based on the plasma coagulation time of normal subjects for the calculation of the prothrombin content of unknown plasma throughout a range of 25 to 400 per cent of normal. The administration of vitamin K to patients without prothrombin deficiency failed to cause significant change

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516. Ferguson, J. H., and Glazko, A. J.: Heparin and Natural Antiprothrombin in Relation to Activation and Assay of Prothrombin, *Am. J. Physiol.* **134**:47, 1941. Glazko, A. J., and Ferguson, J. H.: Quantitative Effects of Immediate Antithrombin, *ibid.* **134**:54, 1941.

517. Ferguson, J. H.: Stability of Prothrombin in Presence of Thrombin, *Proc. Soc. Exper. Biol. & Med.* **46**:80, 1941.

518. Page, R. C., and Russell, H. K.: Prothrombin Estimation Using Russell Viper Venom: Simple Modification of Quick's Method, *J. Lab. & Clin. Med.* **26**:1366, 1941.

519. Crosbie, A., and Scarborough, H.: Activation of Thromboplastin Preparations by Hemolysis and by Lecithin, *Brit. M. J.* **1**:268, 1941.

520. Hobson, F. C. G., and Witts, L. J.: A Venom-Lecithin Reagent for Acceleration of the Clotting Test (Prothrombin Time), *J. Path. & Bact.* **52**:367, 1941.

521. Hause, W. A., and Tocantins, L. M.: Determination of Plasma Prothrombin Variations in Normal Men and Women, *Am. J. Clin. Path.* **11**:54, 1941.

(Rhoads and Norris <sup>522</sup>). Quick <sup>523</sup> assigned a unit value of 100 to the prothrombin content of rabbit's blood. On this scale, that of human blood is given as 20. The prothrombin content of turtle blood is reported by Brambel and Ehrlich <sup>524</sup> to be higher than mammalian values. The prothrombin and the fibrinogen content of the lymph of dogs is one-half the plasma concentration, according to Brinkhous and Walker.<sup>525</sup> Barnes <sup>526</sup> observed no significant alterations of the blood prothrombin content of animals after roentgen irradiation in large and repeated doses. No interference with the absorption of vitamin K compounds by chicks was caused by the oral administration of aluminum hydroxide, according to Fliegelman, Panzer and Rhoads.<sup>527</sup>

Wide variations in the prothrombin content of stored citrated blood and plasma are reported by different investigators. A progressive decline is observed by most of them, although values up to 40 per cent of normal at the end of four months and 100 per cent up to thirteen days are reported by Drew and Scudder.<sup>528</sup> More rapid disappearance of prothrombin was found by Karabin, Udesky and Seed.<sup>529</sup> They report a level of 54 per cent of normal at the end of ten days. The temperature at which blood is stored exerts an important effect on the rate of prothrombin disappearance; according to Rhoads, Warren and Panzer,<sup>430</sup> the rate of disappearance is more rapid at 37 C. than at 4 C.

After the intramuscular injection into dogs of 0.125 to 0.50 Gm. of sodium citrate per kilogram, the prothrombin time determined according to the method of Quick is said by Shafiroff and co-workers <sup>530</sup> to

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522. Rhoads, J. E., and Norris, R. F.: Effect of Vitamin K Therapy on Plasma Prothrombin Level of Patients Without Prothrombin Deficiency, *Bull. Ayer Clin. Lab., Pennsylvania Hosp.* **17**:379, 1941.

523. Quick, A. J.: The Prothrombin Concentration (Determined by the Quick Method) of Various Species, *Am. J. Physiol.* **132**:239, 1941.

524. Brambel, C. E., and Ehrlich, D.: The Prothrombin Activity of Turtle Blood and the Effect of Synthetic Vitamin K Derivatives, *J. Cell. & Comp. Physiol.* **18**:221, 1941.

525. Brinkhous, K. M., and Walker, S. A.: Prothrombin and Fibrinogen in Lymph, *Am. J. Physiol.* **132**:666, 1941.

526. Barnes, W. A.: Prothrombin Formation Following Injury of Bone Marrow by Roentgen Rays, *Am. J. Roentgenol.* **46**:356, 1941.

527. Fliegelman, M. T.; Panzer, L. M., and Rhoads, J. E.: Effect of Colloidal Aluminum Hydroxide on Certain Aspects of Blood Coagulation, *Surgery* **10**:387, 1941.

528. Drew, C. R., and Scudder, J.: Studies in Blood Preservation: Fats of Cellular Elements and Prothrombin in Citrated Blood, *J. Lab. & Clin. Med.* **26**:1473, 1941.

529. Karabin, J. E.; Udesky, H., and Seed, L.: Effect of Stored Citrated Blood Transfusions on Patients with Hypoprothrombinemia, *Surg., Gynec. & Obst.* **73**:10, 1941.

be prolonged. The volume of solution containing the salt was about 50 cc., and the solution was therefore hypertonic. Quick<sup>531</sup> using the same technic observed no such effect.

Studies on the identity of prothrombin by the Tiselius method for obtaining the electrophoretic pattern of plasma proteins are reported by Orr and Moore.<sup>532</sup> A chemical method for the purification of prothrombin obtained from beef plasma was devised by Seegers and Smith.<sup>533</sup>

Some colorimetric reactions of substances possessing vitamin K activity are given by Irreverre and Sullivan,<sup>534</sup> Novelli,<sup>535</sup> Scudi,<sup>536</sup> and Berlin.<sup>537</sup>

Almquist<sup>538</sup> reviews the methods of bioassay of vitamin K compounds, and the biologic unit assigned to active compounds is discussed by Ansbacher.<sup>539</sup>

#### BLOOD CHANGES ASSOCIATED WITH VARIOUS DISORDERS

*Infection.*—The diagnosis of acute appendicitis frequently taxes the acumen of the surgeon to the extreme. For aid he often turns to the blood laboratory for a "white count." The value of the leukocyte count in making a diagnosis of acute appendicitis was investigated by Smith<sup>540</sup> in a series of 93 cases. He finds that in 20 per cent of the cases of acute appendicitis and in fully half of the cases of subacute and chronic appendicitis the number of leukocytes and of neutrophils in the peripheral

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530. Shafiroff, B. G. P.; Doubilet, H., and Co Tui: Effect of Intramuscular Injection of Sodium Citrate on Prothrombin Time of the Blood, *Proc. Soc. Exper. Biol. & Med.* **46**:136, 1941.

531. Quick, A. J.: Prothrombin Level of Blood After Intramuscular Injection of Sodium Citrate, *Proc. Soc. Exper. Biol. & Med.* **47**:1, 1941.

532. Orr, W. F., Jr., and Moore, D. H.: Studies on Identity of Prothrombin, *Proc. Soc. Exper. Biol. & Med.* **46**:357, 1941.

533. Seegers, W. H., and Smith, H. P.: Purification of Prothrombin, *J. Biol. Chem.* **140**:677, 1941.

534. Irreverre, F., and Sullivan, M. X.: A Colorimetric Test for Vitamin K, *Science* **94**:497, 1941.

535. Novelli, A.: A Sensitive Color Reaction for 2-Methyl-1, 4-Naphthoquinone and Related Compounds, *Science* **93**:358, 1941.

536. Scudi, J. V.: A Colorimetric Redox Method for Determination of Vitamin K<sub>1</sub> and Similar Quinones, *Am. J. Physiol.* **133**:440, 1941.

537. Berlin, H.: Simple Method for Determination of 2-Methyl-1, 4-Naphtho-hydroquinone Diacetate, a Substance Exhibiting Vitamin K Activity, *Svensk. kem. tidskr.* **52**:233, 1940; abstracted, *Nutrition Abstr. & Rev.* **11**:209, 1941.

538. Almquist, H. J.: Report on Vitamin K Assay by Curative Biological Test, *J. A. Official Agric. Chemists* **24**:405, 1941.

539. Ansbacher, S.: Editorial Review: Bioassay of Vitamin K, *J. Nutrition* **21**:1, 1941.

540. Smith, C. G.: Value of Leukocyte and Differential Count in Diagnosis of Appendicitis, *Am. J. Clin. Path.* **11**:713, 1941.



blood may be normal. He advises surgeons not to be unduly influenced by normal leukocyte and differential counts.

The use of the Medlar index for prognostication in cases of tuberculous infection is evaluated by Stanbury and Rae,<sup>541</sup> who correlated the progress of 1,401 hospitalized tuberculous patients with their Medlar index at the time of admission. They found that patients with minimal disease show a favorable type of index, while those with far advanced infection predominate in the group with unfavorable indexes. However, patients with favorable indexes tended to improve, regardless of the extent of their tuberculous lesions.

Brown and Otto<sup>542</sup> report confirmatory evidence of eosinophilia occurring early in the course of hookworm infection. Later, if the patient becomes debilitated, the eosinophil count may decrease. In regions in which hookworm infection is endemic a high percentage of eosinophils may be found in persons whose stools do not contain hookworm ova.

In their study of trichinosis Della Vida and Dyke<sup>543</sup> noted that moderate leukocytosis develops at the onset of symptoms and lasts three to four weeks. Secondary leukocytosis occurs later and reaches a maximum in the eleventh week of the disease. Eosinophilia makes its appearance after seven days of symptoms, reaching levels of 20 to 50 per cent. It tapers off by the end of the fourth week and, like the total leukocyte count, shows a secondary rise in the eleventh week of illness. The percentage of lymphocytes remains normal or below normal until the fifth week, when there is a gradual rise through the eleventh week followed by a decline again to normal values. The levels of monocytes and basophils are below normal but tend to rise slightly about the fourth week. The authors correlate the blood findings with the clinical picture as follows: During the first week there is no eosinophilia because these cells are fixed about invading parasites. By the second week surplus eosinophils have been produced, and eosinophilia appears. The cells then decrease while encystment takes place, being grouped about the parasites in the tissue. The secondary rise of the eleventh week represents the liberation of eosinophils from the tissue after encystment has been completed.

Vryonis<sup>544</sup> has carried out extensive studies on erythropoiesis in malaria. He finds that reticulocytosis develops about eight days after

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541. Stanbury, W. S., and Rae, M. V.: The Medlar Index in Pulmonary Tuberculosis, *Am. Rev. Tuberc.* **44**:710, 1941.

542. Brown, H. W., and Otto, G. F.: Differential Leukocyte Count Associated with Hookworm Infection, *Am. J. Dis. Child.* **61**:727 (April) 1941.

543. Della Vida, B. L., and Dyke, S. C.: Blood Picture in Trichiniasis, *Lancet*, **2**:69, 1941.

544. Vryonis, G.: Blood Studies in Malaria: Genesis of Blood Cells in Relation to Treatment with Quinine, *Am. J. M. Sc.* **200**:809, 1940.

the start of quinine therapy, at which time the asexual parasites have disappeared from the blood. The peak of reticulocytosis occurs three days later, and 400,000 to 600,000 cells per cubic millimeter remain in the peripheral blood for seven to nine days. At the time of the reticulocyte peak (eleven days after treatment is started) the red cell count has fallen to its minimum and remains depressed for another week, until the reticulocyte response declines. Subsequently, the red cell count gradually rises to normal. The leukocyte count varies from 7,000 to 16,000 early in the course of therapy. At the time of the reticulocyte peak, on the eleventh day of therapy, the white cell count starts falling and reaches leukocytopenic levels. Neutropenia develops, which lasts until the end of the reticulocyte response (nineteenth day), at which time the neutrophil count again increases to normal and in addition eosinophilia appears. The author believes that erythropoiesis commences after the disappearance of parasitic toxins, while the leukocytopenia is related to a phase of hemopoiesis and not to quinine therapy, since the drug was administered well after the period of white cell decline.

Considerable work has appeared concerning the technic and clinical uses of the erythrocyte sedimentation rate. Wilder<sup>545</sup> has modified the Westergren apparatus and finds it useful in office practice for aid in the diagnosis of rheumatic fever, infectious arthritis, pelvic inflammatory disease, etc. Herzog<sup>546</sup> has used the microsedimentation method of Landow on 405 youthful patients with cardiac disease. Details of the technic are explained. He believes that the upper limits of normal by this method are 18 mm. per hour. Glazer<sup>547</sup> reports a simplified Westergren technic. Agnor<sup>548</sup> analyzes statistics obtained on his series of 2,063 patients. He advocates the use of the blood sedimentation rate as a routine diagnostic laboratory procedure. Sappington and Gillis<sup>549</sup> have used heparin in 1 per cent solution as an anticoagulant and have found that higher sedimentation rates are obtained with heparin than with oxalate solution. These authors suggest that the use of heparin might be advantageous in the Cutler method. Lesser and Kaufman<sup>550</sup> have encountered normal erythrocyte sedimentation rates in 90 per cent of

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545. Wilder, G. B.: Sedimentation Rate of Red Blood Cells: A Simple Office Procedure, with Some Observations from One Thousand Consecutive Office Tests, *J. Indiana M. A.* **34**:24, 1941.

546. Herzog, R. S.: The Microsedimentation Rate, *J. Lab. & Clin. Med.* **27**:355, 1941.

547. Glazer, A. M.: A Simplified Westergren Sedimentation Rate Technique, *J. Lab. & Clin. Med.* **26**:1516, 1941.

548. Agnor, E. B.: Blood Sedimentation Test as Routine Diagnostic Procedure: A Clinical Evaluation of 2,063 Cases, *Ann. Int. Méd.* **14**:774, 1940.

549. Sappington, S. W., and Gillis, L. M.: Heparin as the Anticoagulant in Sedimentation Tests: Comparative Study, *Am. J. Clin. Path.* **11**:83, 1941.

550. Lesser, A., and Kaufman, L. R.: Five Year Survey of Blood Sedimentation Test in Acute Appendicitis, *Surg., Gynec. & Obst.* **73**:163, 1941.

117 cases of acute appendicitis. They believe that this test may be of differential diagnostic value in appendicitis. Fetter and Schnabel<sup>551</sup> failed to observe any significant change in the erythrocyte sedimentation rates during and immediately after fever therapy for dementia paralytica, rheumatoid arthritis, gonococcic arthritis, Sydenham's chorea, ulcerative colitis, rheumatic fever and multiple sclerosis. Altogether 41 patients were studied by them.

In the absence of demonstrable disease 92 per cent of 327 young girls had sedimentation rates between 2 and 13 mm. per hour determined by the Cutler method, according to Benson and Rogers.<sup>552</sup>

Wardle<sup>553</sup> has undertaken experimental studies to determine the reason for the macrocytic type of anemia occurring in persons with *Diphyllobothrium latum* infection. He investigated the clue first offered in 1907, by Faust and Tallquist, who suggested that disintegration products of the tapeworm might be responsible. The author fed lipid fractions extracted from fish tapeworms to normal rabbits and found that the unsaturated fatty acid derivative caused decrease in the erythrocyte and the leukocyte level and an increase in the mean corpuscular volume of the red cells. Fatty acids derived from other sources (oleic acid, stearic acid, etc.) did not have this effect on the blood of rabbits.

From his studies on immunization and virulent infection in tuberculosis in guinea pigs, Birkhaug<sup>554</sup> concludes that the monocyte-lymphocyte ratio and the percentage of monocytes of the peripheral blood are the best indicators of advancing tuberculosis. The earliest response to a tuberculous infection is an increase in monocytes followed shortly by lymphocytopenia.

*Endocrine Dyscrasias.*—Turley and Richter<sup>555</sup> have shown that doses of 1 to 4 grains (0.06 to 0.26 Gm.) of thyroid kill guinea pigs within a few days. If aleuronat (a wheat flour made of aleurone, containing largely protein matter and little starch), a substance which produces lymphocytosis by an unknown mechanism, is administered simultaneously with the large dose of thyroid the guinea pigs do not die. These authors suggest that the artificially produced lymphocytosis somehow protects

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551. Fetter, F., and Schnabel, T. G.: Behavior of Blood Sedimentation Rate During and After Fever Therapy, *Am. J. M. Sc.* **201**:115, 1941.

552. Benson, L., and Rogers, E. J.: Blood Sedimentation Rate in Healthy Girls, *J. Lab. & Clin. Med.* **26**:987, 1941.

553. Wardle, R. A.: Tapeworm Anemia: Influence of Tapeworm Fatty Acid upon the Host Blood Picture, *Tr. Roy. Soc. Canada* **35** (sect. 5):85, 1941.

554. Birkhaug, K.: Allergy and Immunity (Iathergy) in Experimental Tuberculosis: Variations in the Blood Cells of Guinea Pigs Prevented from Ever Becoming Allergic During Immunization with BCG-in-Solid-Paraffin and During Virulent Infection, *Acta tuberc. Scandinav.* **15**:59, 1941.

555. Turley, L. A., and Richter, K. M.: Experimental Study of the Lymphocytic Response in Thyrotoxicosis, *J. Lab. & Clin. Med.* **27**:1, 1941.

the animals against extreme thyrotoxicosis. They do not believe that thyroid reacts directly with aleuronat to neutralize the toxic effect. Vollmer, Gordon, Levenstein and Charipper<sup>556</sup> suggest that the gonadal hormones may account for the sex differences noted in red cell and hemoglobin levels in many species. This is based on the results of experiments on normal, castrated and hypophysectomized rats.

Castrodale, Bierbaum, Helwig and MacBryde<sup>557</sup> administered large equivalent doses of diethylstilbestrol and estradiol to male and female dogs orally and parenterally. Thrombopenia and hemorrhage occurred after either drug was given but more promptly after estradiol. The bone marrow showed an early increase in the number of myeloid elements, followed in some cases by a phase of hypoplasia, reflected in the blood picture by development of anemia, leukocytopenia and thrombopenia. On the other hand, Tyslowitz and Hartman<sup>557</sup> found no toxic hematologic effects after administering large doses of estrogens (estradiol and estrone [theelin]) to rhesus monkeys.

Meyer, Thewlis and Rusch<sup>558</sup> have investigated the relation of the hypophysis to hemopoiesis in rats by removal of various glands of internal secretion and by administration of endocrine and nonspecific substances. They conclude that the hypophysis influences blood formation but that the effect is probably dependent not on a specific hormone but on general metabolic changes.

*Malignant Growths.*—Gruner<sup>559</sup> has studied the total white cell and the differential count at intervals after irradiation in patients with various types of tumors. He found that certain abnormalities of the circulating white cells tended to reappear persistently near the end of thirty-three week cycles and tended to wane in the middle of the cycle. The abnormalities noted were leukocytosis (up to 12,000 cells), monocytosis and lymphocytopenia. Bizarre nuclei and inclusion bodies were observed in the monocytes. Metastatic lesions also tended to manifest themselves at the end of cycles of thirty-three weeks or multiples of thirty-three weeks. This phenomenon was first described by Webster in 1938. Therefore, a periodicity of the malignant tumor with thirty-three week cycles of activity may be reflected by leukocyte abnormalities.

556. Vollmer, E. P.; Gordon, A. S.; Levenstein, I., and Charipper, H. A.: Effects of Sex and Gonadotropic Hormones on Red Cell Counts of Rats, *Proc. Soc. Exper. Biol. & Med.* **46**:409, 1941.

557. Tyslowitz, R., and Hartman, C. G.: Influence of Large Doses of Estrogens on the Blood Picture of Rhesus Monkeys (*Macaca Mulatta*), *Endocrinology* **29**:349, 1941.

558. Meyer, O. O.; Thewlis, E. W., and Rusch, H. P.: The Hypophysis and Hemopoiesis, *Endocrinology* **27**:932, 1940.

559. Gruner, O. C.: Periodic Fluctuations in Blood Picture in Cancer and Their Bearing on Radiation Therapy, *Canad. M. A. J.* **44**:256, 1941.

Feldman <sup>560</sup> has noted that although the sedimentation rate of erythrocytes usually tends to decrease as the blood ages, in cases of Hodgkin's disease and malignant tumors the sedimentation rate of blood determined twenty-four hours after venipuncture equals or exceeds the measurement obtained when the blood is freshly drawn. This phenomenon is termed "maintenance of sedimentation rate." Of 118 patients with proved malignant growths, 96 per cent "maintained" their sedimentation rate for the twenty-four hour period, whereas of 55 patients with increased rate of erythrocyte sedimentation not due to a malignant growth, absence of the "maintenance" was observed in 95 per cent. The technic is given in detail.

In rat and mouse experiments both with benign and with malignant types of tumors, there developed an elevation of the white cell count which depended on the organismal differential of hosts and transplants, according to Blumenthal.<sup>561</sup> When homoisotransplants attain a large size, the animals become debilitated and anemia develops, with secondary hyperplasia of the marrow. Ohga, Jo and Fujii <sup>562</sup> produced anemia by bleeding in healthy dogs and in others with sarcoma tumors. They found that the dogs with sarcoma regenerated red cells and hemoglobin more slowly than the normal animals. They demonstrated that in their experiments the bone marrow was not actually invaded by a malignant growth but that the poor erythropoiesis was most likely explained on the basis of toxic changes which made the whole organism less efficient.

*Chemical Intoxication.*—The blood abnormalities most commonly encountered in workers exposed to benzene are listed by Goldwater <sup>563</sup> as anemia with relatively high hemoglobin values, thrombopenia and, occasionally, leukocytopenia. Goldwater and Tewksbury,<sup>564</sup> who studied over 100 subjects, found some of these effects to persist for as long as two years after exposure. Schwarz and Teleky <sup>565</sup> observed thrombopenia as an early sign of toxicity in workers exposed to benzene.

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560. Feldman, H.: Maintenance of the Sedimentation Rate of Erythrocytes in Vitro in Cases of Malignant Tumors and Hodgkin's Disease, *Am. J. M. Sc.* **200**:820, 1940.

561. Blumenthal, H. T.: Effects of Spontaneous and Transplanted Rat and Mouse Tumors on the Red and White Cells in Circulating Blood and Bone Marrow, *Cancer Research* **1**:196, 1941.

562. Ohga, T.; Jo, S., and Fujii, Y.: Einflüsse der malignen Geschwülste auf die hämatopoetischen Organen; Einfluss der malignen Geschwülste auf die Genesung von der künstlichen Anämie, *Taiwan Igakkai Zassi* **40**:1254, 1941.

563. Goldwater, L. J.: Disturbances in Blood Following Exposure to Benzol, *J. Lab. & Clin. Med.* **26**:957, 1941.

564. Goldwater, L. J., and Tewksbury, M. P.: Recovery Following Exposure to Benzene (Benzol), *J. Indust. Hyg. & Toxicol.* **23**:217, 1941.

565. Schwarz, E., and Teleky, L.: Some Facts and Reflections on Problem of Poisoning by Benzene and Its Homologs, *J. Indust. Hyg. & Toxicol.* **23**:1, 1941.

Hamilton-Paterson,<sup>566</sup> in a review of the literature, concludes that leukocytopenia and anemia occur most frequently in chronic intoxication. Aubertin<sup>567</sup> reaches the same conclusion in a similar review. The destructive action of benzene on the bone marrow is particularly emphasized by the two last-named authors.

Schrenk and his collaborators<sup>568</sup> found the highest concentration of benzene in the fat and the bone marrow of dogs exposed to toxic fumes of benzene. The concentration of benzene was twenty times greater in the bone marrow than in the peripheral blood. In rabbits a fall in the red cell count two hours after exposure to benzene vapor was noted by Robinson and Climenko.<sup>569</sup> Latta and Davies<sup>570</sup> noted in rats an initial stimulation of granulopoiesis in the bone marrow after exposure to benzene fumes. Large or repeated exposure caused granulocytopenia and in time aplastic bone marrow.

Lead hazards in the printing industry were studied by Ruf and Belknap<sup>571</sup> and by Kehoe.<sup>572</sup> No appreciable lead hazard was found in the case of workers in the composing room. After exposures of five years, no blood abnormalities were observed in 40 subjects studied by Ruf and Belknap. Kammer<sup>573</sup> examined 250 workers in the lead-bearing steel (ledloy) industry. No evidence of plumbism was found in the blood or the urine or by physical examination.

Marchmont-Robinson<sup>574</sup> determined the urinary excretion of lead in workers exposed to lead dust. He observed a significant clinical regres-

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566. Hamilton-Paterson, J. L.: Chronic Benzene Poisoning, *Lancet* **1**:73, 1941.

567. Aubertin, C.: Le benzène, agent leucolytique, *Paris méd.* **2**:504, 1940.

568. Schrenk, H. H., and others: Absorption, Distribution and Elimination of Benzene by Body Tissues and Fluids of Dogs Exposed to Benzene Vapor, *J. Indust. Hyg. & Toxicol.* **23**:20, 1941.

569. Robinson, E. J., and Climenko, D. R.: Effects of Inhalation of Benzene Vapors on Red Blood Cells of Rabbits, *J. Indust. Hyg. & Toxicol.* **23**:232, 1941.

570. Latta, J. S., and Davies, L. T.: Effects on Blood and Hemopoietic Organs of Albino Rat of Repeated Administration of Benzene, *Arch. Path.* **31**:55 (Jan.) 1941.

571. Ruf, H. W., and Belknap, E. L.: Studies on the Lead Hazards in Certain Phases of Printing: I. Actual Lead Exposures as Measured by the Amount of Lead in Printing Atmospheres; II. Actual Lead Absorption as Measured by Physical Examinations, Blood and Urine Studies, *J. Indust. Hyg. & Toxicol.* **22**:445, 1940.

572. Kehoe, R. A.: Note on "Studies of the Lead Hazards in Certain Phases of Printing," *J. Indust. Hyg. & Toxicol.* **23**:159, 1941.

573. Kammer, A. G.: Studies of Workers Exposed During Production of Lead Bearing Steel (Ledloy), *J. Indust. Hyg. & Toxicol.* **23**:93, 1941.

574. Marchmont-Robinson, S. W.: Effect of Vitamin C on Workers Exposed to Lead Dust, *J. Lab. & Clin. Med.* **26**:1478, 1941.

sion of symptoms and a slight increase in lead excretion after the daily oral administration of 50 mg. of ascorbic acid. The author suggests that many of the vague symptoms associated with chronic plumbism are evidences of subclinical scurvy. The presence of lead may interfere with vitamin C absorption, and the author suggests that a vitamin C deficiency may be prevented by increasing the ascorbic acid intake. Kety and Letonoff,<sup>575</sup> in a preliminary report, noted rapid disappearance of toxic symptoms in patients with lead poisoning who were given sodium citrate by mouth. The administration of 6 to 12 Gm. in divided daily doses was followed by a fall in the concentration of lead in the blood in all cases.

Industrial manganese poisoning is accompanied by leukocytopenia with neutropenia, according to Flinn, Neal and Fulton.<sup>576</sup> The authors observed normal red cell and platelet counts in the 50 workers studied.

Brieger<sup>577</sup> reviews the literature of carbon disulfide intoxication. He concludes that further study is needed before this agent is classed as a blood intoxicant.

The increased use of thiocyanate preparations in clinical medicine prompted Lindberg, Wald and Barker<sup>578</sup> to undertake toxicologic studies of this agent on dogs. Potassium thiocyanate was given orally to 12 dogs in amounts sufficient to raise the blood level to 20 to 60 mg. per hundred cubic centimeters. For human beings a level of 8 to 14 mg. per hundred cubic centimeters is considered safe. Severe microcytic, hypochromic anemia developed in the animals, while the white cell and differential counts, red cell fragility and icterus index were unaffected. Blood cholesterol and serum protein values decreased, and the color index and the volume index of red cells fell below 0.8. Pathologic examination revealed damage of the bone marrow and the liver.

#### METHODS AND MISCELLANEOUS MATERIAL

The structure and properties of the human erythrocyte are discussed by Haden.<sup>579</sup> The article includes excellent bas-relief photographs of red

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575. Kety, S. S., and Letonoff, T. V.: Treatment of Lead Poisoning with Sodium Citrate, *Proc. Soc. Exper. Biol. & Med.* **46**:476, 1941.

576. Flinn, R. H.; Neal, P. A., and Fulton, W. B.: Industrial Manganese Poisoning, *J. Indust. Hyg. & Toxicol.* **23**:374, 1941.

577. Brieger, H.: Effects of Carbon Disulfide on Blood Corpuscles, *J. Indust. Hyg. & Toxicol.* **23**:388, 1941.

578. Lindberg, H. A.; Wald, M. H., and Barker, M. H.: Observations on Pathologic Effects of Thiocyanate: Experimental Study, *Am. Heart J.* **21**:605, 1941.

579. Haden, R. L.: Human Red Blood Cell (Porter Lecture), *Cleveland Clin. Quart.* **8**:111, 1941.

cells. The following formula is suggested by Vallarino<sup>580</sup> as an improved dilution fluid for the enumeration of erythrocytes: iodine, 0.3 per cent; potassium iodide, 0.4 per cent; sodium citrate ( $\text{Na}_2\text{C}_6\text{H}_5\text{O}_7 \cdot 2\text{H}_2\text{O}$ ), 1 per cent; add distilled water to 100 cc., and filter. A study of some of the factors involved in calculating erythrocyte counts and percentage volume by opacimetry is reported by Ponder.<sup>581</sup> He states that opacity is a function of several variables and that prediction of counts is poor, even in the case of normal blood. The standard error of discrepancies between the count obtained by enumeration and that secured by opacimetry is about  $\pm 500,000$  and that for the percentage volume is about  $\pm 2.7$  units of volume. For opacity measurements an isotonic solution of sodium citrate with a 0.1 per cent solution of formaldehyde U. S. P. is preferable to an isotonic solution of sodium chloride, but only because the variations in light transmission which accompany stirring are greatly lessened. The stirring effects seem to be due to the orientation of masses of cells by currents in the suspension medium.

The measurement of red cell diameter by a diffractometric method is reported by Smith.<sup>582</sup> A simple device attached to an ordinary microscope was employed. The results obtained on the same specimens of blood by two examiners were in reasonably close agreement. A micromethod for the determination of erythrocyte fragility which involves the use of only six concentrations of sodium chloride is described by Kato.<sup>583</sup> Greatly increased fragility of red cells was observed in an infant with erythroblastosis foetalis. As the number of circulating nucleated erythrocytes was reduced, the resistance of the red cells to hypotonic solution of sodium chloride became normal.

The circulating and the total red cell volume of dogs have been measured by Hahn and his associates<sup>584</sup> with the aid of radioactive iron. The red cell mass calculated by means of this isotope averages about 20 per cent less than the value obtained from determinations of the plasma volume and the hematocrit reading of blood from the jugular vein. A

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580. Vallarino, L. A.: An Improved Dilution Fluid for Erythrocyte Counts, *Stain Technol.* **16**:177, 1941.

581. Ponder, E.: Red Cell Counts, Percentage Volume, and Opacity of Suspensions, *Am. J. Physiol.* **134**:739, 1941.

582. Smith, K. E.: The Measurement of Red Blood Cell Diameter by the Diffractometer, *J. Lab. & Clin. Med.* **26**:696, 1941.

583. Kato, K.: A Simple and Accurate Microfragility Test for Measuring Erythrocyte Resistance: A Combination Microhemopipette Method, *J. Lab. & Clin. Med.* **26**:703, 1941.

584. Hahn, P. F.; Balfour, W. M.; Ross, J. F.; Bale, W. F., and Whipple, G. H.: Red Cell Volume Circulating and Total as Determined by Radio Iron, *Science* **93**:87, 1941.



number of articles dealing with the determination of plasma and of total blood volume, the cell-plasma ratio in different parts of the circulation and the restoration of blood volume after acute blood loss have been published by Stead, Ebert and Gibson.<sup>585</sup> Adequate consideration of their data would require more space than can be devoted to the subject in this review, and the interested reader will find it profitable to consult the original articles. Brines, Gibson and Kunkel<sup>586</sup> state that the total blood volume at birth is about 300 cc. During the first year the quantity of circulating blood is doubled, and thenceforth the volume increases to a value of about 2,500 cc. for both sexes at puberty. The plasma and the total blood volume bear a closer relation to size than to age. The unit volume per kilogram of body weight or square meter of surface area is not a constant but increases with growth. The plasma, the red cell and the total blood volume may be predicted, according to the authors, in the case of normal infants and children, on the basis of height, weight or surface area. A method for the measurement of red cell volume in blood by the use of Evans blue dye is described by Shohl and Hunter.<sup>587</sup>

A study of the familial incidence of elliptic erythrocytes is reported by Wyandt, Bancroft and Winship.<sup>588</sup> The authors observed the peculiarly shaped red cells in the blood of 86 members of 3 interrelated families of pure German extraction. In 1 member only of each of 2 pairs of twins were oval erythrocytes found. Aspiration of sternal marrow performed on 2 subjects with ovalocytosis revealed spherical nucleated erythrocytes. The evidence indicates that the change to an elliptic form occurs during or after the reticulocyte stage of development. The red cell abnormality is compatible with long life and is not correlated with the incidence of any recognized disease.

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585. Stead, E. A., Jr., and Ebert, R. V.: Relationship of the Plasma Volume and the Cell Plasma Ratio to the Total Red Cell Volume, *Am. J. Physiol.* **132**:411, 1941. Ebert, R. V., and Stead, E. A., Jr.: Demonstration That the Cell Plasma Ratio of Blood Contained in Minute Vessels Is Lower Than That of Venous Blood, *J. Clin. Investigation* **20**:317, 1941. Ebert, R. V.; Stead, E. A., Jr., and Gibson, J. G., II: Response of Normal Subjects to Acute Blood Loss, with Special Reference to the Mechanism of Restoration of Blood Volume, *Arch. Int. Med.* **68**:578 (Sept.) 1941. Ebert, K. V., and Stead, E. A., Jr.: An Error in Measuring Changes in Plasma Volume After Exercise, *Proc. Soc. Exper. Biol. & Med.* **46**:139, 1941.

586. Brines, J. K.; Gibson, J. G., II, and Kunkel, P.: The Blood Volume in Normal Infants and Children, *J. Pediat.* **18**:447, 1941.

587. Shohl, A. T., and Hunter, T. H.: The Measurement of Cell Volume of Blood by the Evans Blue Dye Method, *J. Lab. & Clin. Med.* **26**:1829, 1941.

588. Wyandt, H.; Bancroft, P. M., and Winship, T. O.: Elliptic Erythrocytes in Man, *Arch. Int. Med.* **68**:1043 (Dec.) 1941.

A genetic study of persons with oval red cells was carried out by Burks and Wyandt.<sup>589</sup> They report the possibility of incomplete sex linkage between oval cells and the presence of AB agglutinogens.

Erythrocytes which show blue granules when treated with potassium ferrocyanide and hydrochloric acid, the prussian blue reaction, are described by Grüneberg.<sup>590</sup> Such granules are found in the cells of mouse and rat embryos, and after birth about 4 per cent of the circulating erythrocytes contain them. Large numbers of the granular erythrocytes were found in mice with the recessive gene for flexed tail and belly spot associated with normocytic anemia.

A comparison of various methods of hemoglobin determination was made by Karr and Clark,<sup>591</sup> and many of the results obtained were considered grossly inaccurate. Standardized photoelectric methods are recommended. Barkan<sup>592</sup> describes a method for the estimation of hemoglobin by the use of undiluted reduced blood, which avoids errors due to variations of the time of reading. The hemoglobin contents of ear and of finger blood were compared with that of venous blood by Sørensen.<sup>593</sup> Samples removed immediately after ear puncture were, in general, found to yield erroneously high results, and more accurate determinations were made on blood from the finger. Isaacs<sup>594</sup> proposes that the quantity of hemoglobin expressed in grams per hundred cubic centimeters be multiplied by the factor 3 and the product divided by the erythrocyte count expressed in hundreds of thousands per cubic millimeter, in order to obtain an index possessing the same significance as the color index, but not requiring conversion of absolute values to percentages. A commonly employed and more accurate method of rapidly securing an approximation of the color index consists of dividing

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589. Burks, B. S., and Wyandt, H.: Oval Blood Cells in Human Subjects Tested for Linkage with Taste for PTC, Mid-Digital Hair, Hair Color, AB Agglutinogens and Sex, *Genetics* **26**:223, 1941.

590. Grüneberg, H.: Siderocytes: New Kind of Erythrocytes, *Nature*, London **148**:114, 1941.

591. Karr, W. G., and Clark, J. H.: Comparison of Various Hemoglobin Methods as Performed in Hospital and Physicians' Laboratories, *Am. J. Clin. Path., Tech. Supp.* **5**:127, 1941.

592. Barkan, G.: Hemoglobin Estimation with Undiluted Reduced Blood, *J. Lab. & Clin. Med.* **26**:1823, 1941.

593. Sørensen, G.: Variations in the Hemoglobin Content of Capillary Blood and Their Significance in the Technique of Hemoglobin Determination, *Nord. med. (Hospitaltid.)* **10**:1117, 1941; abstracted, *Nutrition Abstr. & Rev.* **11**:185, 1941.

594. Isaacs, R.: Simple Hemoglobin-Red Blood Cell Ratio to Replace Color Index, *J. A. M. A.* **116**:2258 (May 17) 1941.

the gram value of hemoglobin per hundred cubic centimeters of blood by three times the erythrocyte count expressed in millions per cubic millimeter.

Ramsey<sup>595</sup> reports evidence of two types of hemoglobin in the blood of various mammals, birds, reptiles and amphibia. The types differ in their resistance to alkaline denaturation. Denaturation was hastened either by increasing the degree of alkalinity or by raising the temperature of the medium.

Values for the concentration of hemoglobin in the blood are reported by Wardlaw<sup>596</sup> and by Meccheri<sup>597</sup> for normal men and by Ta<sup>598</sup> for women in India. Hematologic values in elderly patients are reported by Fowler and his co-workers.<sup>599</sup> Less difference between the sexes was observed in them than is encountered in younger persons, and presence or absence of gastric hydrochloric acid seemed not to be related to the observed blood levels.

Changes in the white cell count during labor and in the early postpartum period were investigated by Wolff.<sup>600</sup> He observed progressive leukocytosis, which appeared to be related to uterine contractions, since no rise occurred during periods of inertia of the uterus.

In 4 of 8 cases of gargoylism Reilly<sup>601</sup> noted peculiar granules in the white cells. The neutrophils were most often affected, but similar changes were also found in lymphocytes and monocytes. When stained with Wright's stain such granules were usually larger than those of normal neutrophils and were tinted lilac blue, but in some cells eosinophilic granules, smaller and less refractile than those of normal eosinophils, were observed. The granules were found in cells contained within the peripheral blood, the bone marrow and the spleen. The author suggests that they may represent a type of toxic reaction.

Blood studies made on a series of patients with intestinal obstruction revealed leukocytopenia developing at some time during the first week

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595. Ramsey, H. J.: A Comparative Study of Hemoglobin Denaturation, *J. Cell. & Comp. Physiol.* **18**:369, 1941.

596. Wardlaw, H. S. H.: Concentration of Haemoglobin in Blood of Normal Men, *M. J. Australia* **2**:103, 1941.

597. Meccheri, L. A.: Blood Hemoglobin Concentration in Healthy Persons and in Persons with Pulmonary Tuberculosis, *Publ. d. Centro de invest. tisiol.* **4**:83, 1940.

598. Ta, C. R.: Haematological Studies in Indians: Normal Indian Women in Calcutta, *Indian J. M. Research* **29**:375, 1941.

599. Fowler, W. M.; Stephens, R. L., and Stump, R. B.: Changes in Hematological Values in Elderly Patients, *Am. J. Clin. Path.* **11**:700, 1941.

600. Wolff, J. R.: Leukocyte Count in Labor, *Am. J. Obst. & Gynec.* **41**:611, 1941.

601. Reilly, W. A.: Granules in the Leukocytes in Gargoylism, *Am. J. Dis. Child.* **62**:489 (Sept.) 1941.

after the surgical release of such obstruction, according to Harris and Feldheim.<sup>602</sup> The white cell counts decreased from a moderately elevated level before operation to a range of 2,000 to 3,000 per cubic millimeter during the postoperative period. Relative neutropenia of moderate degree occurred. The changes are attributed to the presence of toxins within the obstructed bowel which are not absorbed because of capillary compression until the obstruction is released. When leukocytopenia occurs before operation, it is believed to indicate that only partial obstruction is present, thus enabling absorption of toxins to take place.

Graham and Fowler<sup>603</sup> state that transfused leukocytes contained in freshly obtained donors' blood disappear from the circulation of the recipient during a period of two and one-half hours. Although in stored blood the white cells undergo disintegration, the leukocyte products so formed may have a stimulative action on new white cell production. However, no definite evidences of such stimulation were observed by the authors during the observation of 15 patients with various types of infection.

Leukocytosis with a shift to younger forms of neutrophils was observed by Curphey and Ponder<sup>604</sup> during the course of experimentally produced shock.

The leukocytes of a number of primitive species of invertebrates, as well as those of vertebrates, were studied by George.<sup>605</sup> In all species examined the leukocytes appeared to exist as free cells of mesenchymal origin. In many low forms they performed the important functions of food handling and digestion, as well as possessing, in common with the white cells of higher animals, the property of phagocytosis of harmful substances. Turpin and his associates<sup>606</sup> studied the Arneth leukocyte formulas of a number of sets of twins. They found the same white cell patterns in both members of pairs of identical twins and varying formulas in the case of heterozygous twins.

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602. Harris, F. I., and Feldheim, J. S.: Leukocyte Exhaustion in Intestinal Obstruction, *Am. J. Surg.* **54**:417, 1941.

603. Graham, J. A., and Fowler, W. M.: Behavior of the Recipient's Leukocyte Count Following Transfusion of Preserved Blood, *J. Lab. & Clin. Med.* **26**:1911, 1941.

604. Curphey, T. J., and Ponder, E.: Leukocyte Response in Experimental Shock, *Am. J. Path.* **17**:602, 1941.

605. George, W. C.: Comparative Hematology and the Functions of the Leukocytes, *Quart. Rev. Biol.* **16**:426, 1941.

606. Turpin, R.; Caratzali, A., and Piton, J.: De l'influence de l'hérédité sur la formule d'Arneth, *Presse méd.* **48**:538, 1940.

Consideration of the numerous articles which deal with the performance of the sedimentation test and report results obtained with this laboratory procedure are omitted from this review. An authoritative discussion of the subject of the sedimentation phenomenon and its application to clinical practice has been presented by Wintrobe.<sup>607</sup>

Articles dealing with the blood platelets and the factors involved in the coagulation of the blood have been reviewed in the section on hemorrhagic disorders. Diagnostic tests based on alterations of the leukocytes and studies made by aspiration of sternal marrow have likewise been considered elsewhere. Two hundred and nine articles appearing in the literature from July 1, 1939 to June 30, 1940 on the formed elements of the blood have been reviewed by Higgins.<sup>608</sup>

The Thomas Henry Simpson Memorial Institute for Medical Research.

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607. Wintrobe, M. M.: Erythrocyte Sedimentation Test, *Am. J. Clin. Path.* **11**:562, 1941.

608. Higgins, G. M.: Formed Elements of Blood, *Ann. Rev. Physiol.* **3**:283, 1941.

## Book Reviews

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**Diseases of the Blood and Atlas of Hematology.** By Roy R. Kracke, M.D. Second edition, revised and enlarged. Price, \$15. Pp. 692, with 46 illustrations and 54 colored plates. Philadelphia: J. B. Lippincott Company, 1941.

This book combines a textbook, a laboratory guide and an atlas of hematology.

The material is grouped in eight sections: Hematologic Terminology, the Development and Morphology of Blood Cells, Leukocytosis and Leukopenia, the Anemias, the Leukemias, Hemorrhagic Diseases, Miscellaneous, and Hematologic Technic.

A separate chapter has been contributed by Dr. Lloyd F. Craver on the treatment of leukemia, including recent advances in the use of irradiation and radioactive isotopes. Dr. Francis P. Parker has a chapter on blood groups and blood transfusions; Dr. Elizabeth Gambrell, a chapter on malaria, and Dr. R. P. Custer, a section on bone marrow.

The first forty pages are devoted to a discussion of hematologic terminology in which the author starts a crusade for a more fundamental understanding of this perplexing problem. It is questionable if such a crusade belongs in a book of this type. In the chapter on classification of anemias, the author propounds both the morphologic classification of Osgood, Wintrobe and Haden and the clinical etiologic classification of Castle and Minot. But in the subsequent chapter the author fails to abide by either classification and groups a long list of anemias under the general heading of hypochromic anemias. This seems neither justified nor good teaching. The reviewer feels that the author should have exerted more right of editorship in regard to the contributed chapters. For example, in the chapter on bone marrow a complete repetition of the discussion of terminology, cell morphology and origin and development of cells is given, which only adds to the state of confusion that the author had so nobly attempted to straighten out in earlier chapters. The chapter on malaria, although excellent, is considerably longer than chapters on the essential anemias. The selection of bibliography is excellent, although the reviewer could mention a few outstanding omissions, particularly Bernstein's review of infectious mononucleosis, which appeared in the *Journal of Medicine*. As a whole, the reviewer feels that the book has a definite place in American hematology and certainly can be recommended.

**Medical Progress, 1940: A Series of Fifty-Two Reports Published During 1940 in The New England Journal of Medicine.** Edited by Robert N. Nye, M.D. Price, \$4. Pp. 625. Springfield, Ill.: Charles C. Thomas, Publisher, 1941.

The reviewer has followed with interest the articles that have appeared in the *New England Journal of Medicine* dealing with advances in diagnosis and therapy in the fields in which the authors were particularly interested. These reviews have been of great value to the teacher employing them as references for reading by senior medical students. Comments from practitioners of medicine have shown that the articles have been valuable to them.

It might be said that these papers, strictly speaking, are not attempts to cover all the recent literature on particular subjects. An author picks out the high spots and mentions only those contributions in current medical literature which he as a critic and one who knows his subject well can evaluate as being worth while and representing distinct advances in knowledge of diseases, functional disorders, pathologic conditions or any other aspect of the subject.

This present, or second, edition, represents in one volume the reviews (it might possibly be better to speak of them as discussions) of particular subjects which appeared in the *New England Journal of Medicine* during 1940. The book can be recommended most highly not only to the readers already mentioned but to the specialist who would be interested in a brief summary of the important contribu-

tions in specialties other than the one with which he is thoroughly familiar. The format of the book is excellent; particularly to be commended are the extensive bibliographies.

**Clinical Roentgenology of Pregnancy.** By William Snow, M.D., Director of Radiology, Bronx Hospital, and Roentgenologist-in-Charge, Harlem Hospital. Price, \$4.50. Pp. 178, with 119 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1942.

The author states in the preface that the roentgen study of pregnancy is fulfilling an everyday need which he claims is easily as important as the need for other major roentgen studies, such as those of the respiratory, the gastrointestinal and the urinary tract. He has prepared this book as a short text by which to make the clinical roentgenology of pregnancy more generally useful.

The seven chapters begin, by way of introduction, with a general discussion of the use of the roentgen ray in pregnancy. There is a good deal here to interest the internist.

Five following chapters deal with the more strictly technical aspects of the book's subject. The last chapter comprises case reports: On one page are roentgenograms, and on the opposite page are short case summaries, which describe exactly the manner in which each roentgenogram is to be interpreted in connection with the given history.

The entire volume is well prepared in legible type, with clear tables and good film reproductions, which are labeled plainly so as to be as understandable as possible. The author hopes that his book will be used as a working manual and as a ready reference by those interested in the roentgenology of pregnancy. In all probability this wish will be satisfied.

**Cerebrospinal Fever.** By Denis Brinton, D.M. (Oxon.), F.R.C.P. (Lond.). Price, \$3. Pp. 172. Baltimore: Williams & Wilkins Company, 1941.

This little book from England, of some one hundred and fifty pages of text, should at the present time be of considerable importance for two reasons. In the first place, meningitis is an ever present disease which might, if the experiences of the last war are repeated, increase to large proportions in cantonments. The second reason is that the book contains a full description of the modern treatment of the disease, particularly with chemotherapeutic agents in the last two years. The reduction in the mortality of meningitis as a result of the use of sulfanilamide and its derivatives has been so remarkable that every physician should be thoroughly acquainted with methods of treatment which have already proved of such value.

Brinton discusses fully the usual features that one would expect in a systematic outline of the disease. Epidemiology, etiology, pathology, course, diagnosis and so on compose roughly about half the book. The remainder is given over to treatment. There is a rather small list of references at the end of the text. The advice that the author gives in regard to treatment is excellent; the presentation of the remainder of the various phases of cerebrospinal fever is conservative and more or less of the conventional textbook type. The book itself is well printed, and the format leaves nothing to be desired.

**Neural Mechanisms in Poliomyelitis.** By Howard A. Howe and David Bordian. Price, \$3.50. Pp. 234, with 39 plates. New York: The Commonwealth Fund, 1942.

This important monograph by outstanding investigators in the field of poliomyelitis presents the evidence for transmission of virus on the basis both of original work and of review of the literature. The paramount importance of neural transmission even when the portal of entry is in the gastrointestinal tract is elucidated. In general, the relative importance of the respiratory tract and the alimentary tract as routes of invasion in different species of monkeys and in man is discussed, and gaps in knowledge not yet filled are pointed out. Of especial interest, of course, is the detailed account of the authors' own experiments, illustrated by many photomicrographs.

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